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<p>(21) International Application Number: PCT/KR99/00213 (22) International Filing Date: 1 May 1999 (01.05.99) (30) Priority Data: <table border="0"> <tr> <td>1998/17153</td> <td>13 May 1998 (13.05.98)</td> <td>KR</td> </tr> <tr> <td>1998/19555</td> <td>28 May 1998 (28.05.98)</td> <td>KR</td> </tr> <tr> <td>1998/28258</td> <td>14 July 1998 (14.07.98)</td> <td>KR</td> </tr> </table> <p>(71) Applicant (for all designated States except US): DONG WHA PARM. IND. CO., LTD. [KR/KR]; 5, Soonwha-dong, Joong-ku, Seoul 100-130 (KR). (72) Inventors; and (75) Inventors/Applicants (for US only): YOON, Sung, Joon [KR/KR]; 1420-11, Sillim-5dong, Kwanak-ku, Seoul 151-015 (KR). LEE, Sang, Wook [KR/KR]; 105-1601, Keumho Apt., 149-1, Bakdal-2dong, Manan-ku, Anyang, Kyungki-do 430-032 (KR). SIM, Hyeong, Su [KR/KR]; 356-211, Jookong Apt., 35, Chamsil-dong, Songpa-ku, Seoul 138-220 (KR). PARK, Yong, Kyun [KR/KR]; 103-1804, Seohae Apt., 138 Block, Eunhaengjiku, Daeya-dong, Shiheung, Kyungki-do 429-010 (KR). YANG, Wang, Yong [KR/KR]; 427-25, Anyang-6dong, Manan-ku, Anyang, Kyungki-do 430-016 (KR). KIM, Jong, Woo [KR/KR]; 305-28, Bisan-3dong, Dongan-ku,</p> </p>		1998/17153	13 May 1998 (13.05.98)	KR	1998/19555	28 May 1998 (28.05.98)	KR	1998/28258	14 July 1998 (14.07.98)	KR	<p>Anyang, Kyungki-do 431-053 (KR). HAN, Jae, Jin [KR/KR]; 12-502, Poil-Jookong Apt., 623, Naeson-1dong, Yiwang, Kyungki-do 437-081 (KR). YOON, Je, In [KR/KR]; 2541-1, Keumkwang-2dong, Joongwon-ku, Sungnam, Kyungki-do 462-242 (KR). PARK, Sang, Jin [KR/KR]; 316, Keumho Apt., 44, Cheonho-1dong, Kangdong-ku, Seoul 134-021 (KR). PARK, Hee, Jeoung [KR/KR]; 68-79, Bakdal-dong, Manan-ku, Anyang, Kyungki-do 435-010 (KR). SIN, Dong, Hyuk [KR/KR]; 402-2003, Jookong Apt., 885, Dang-dong, Kunpo, Kyungki-do 435-010 (KR). CHANG, Hwan, Bong [KR/KR]; 12/1, 135-7, Bupyung-2dong, Bupyung-ku, Incheon 403-012 (KR). (74) Agent: HUH, Sang, Hoon; Hyecheon Building, 13th floor, Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR). (81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
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<p>(54) Title: NOVEL 2,5-PYRIDINEDICARBOXYLIC ACID DERIVATIVES</p> <div style="text-align: center;"> <p style="text-align: right;">(1)</p> </div> <p>(57) Abstract</p> <p>The present invention relates to novel 2,5-pyridinedicarboxylic acid derivatives and more particularly, to novel 2,5-pyridinedicarboxylic acid derivatives of formula (1) and its pharmaceutically acceptable salts as anti retroviral agents, having inhibitory activities against the proliferation of retrovirus such as hepatitis B virus and human immunodeficiency virus, including its preparing method, wherein, R₁, R₂, R₃ and n are the same as defined in the detailed description of the invention, respectively.</p>											

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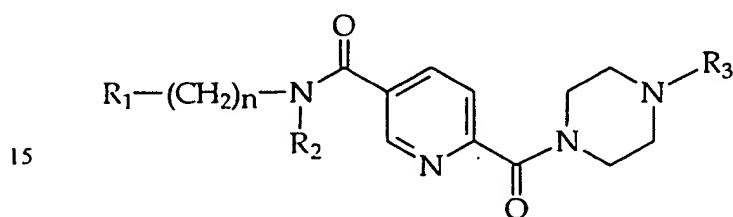
NOVEL 2,5-PYRIDINEDICARBOXYLIC ACID DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention relates to novel 2,5-pyridinedicarboxylic acid derivatives and more particularly, to novel 2,5-pyridinedicarboxylic acid derivatives of the following formula 1 and its pharmaceutically acceptable salts as anti retroviral agents, having inhibitory activities against the proliferation of retrovirus such as hepatitis B virus and human
10 immunodeficiency virus, including its preparing method:

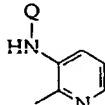
Formula 1



wherein, R₁ represents hydroxy group, straight or branched alkyl group of 1 to 6 carbon atoms, cycloalkyl group of 3 to 6 carbon atoms unsubstituted or substituted with alkyl group of 1 to 3 carbon atoms, alkyl
20 group of 1 to 3 carbon atoms substituted with cycloalkyl group of 3 to 6 carbon atoms, straight or branched hydroxyalkyl group of 1 to 6 carbon atoms, straight or branched dihydroxyalkyl group of 3 to 6 carbon atoms, straight or branched alkoxy group of 1 to 4 carbon atoms, hydroxyalkoxy group of 2 to 4 carbon atoms, straight or branched alkoxyalkyl group of 2 to 6 carbon atoms,
25 dialkoxyalkyl group of 3 to 6 carbon atoms, dialkylamino group of 2 to 4 carbon atoms, acetylamino group, vinyl group, or saturated or unsaturated five or six membered heterocyclic ring having 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur; hence, the heterocycle is unsubstituted or substituted with same or different 1~3

substituents selected from the group consisting of alkyl group of 1 to 3 carbon atoms, alkoxy group of 1 to 3 carbon atoms, hydroxyalkyl group of 1 to 3 carbon atoms, phenyl group, carbamoyl group and hydroxy group;

R_2 represents hydrogen atom, phenyl group, straight or branched alkyl group of 1 to 4 carbon atoms, straight or branched hydroxyalkyl group of 2 to 4 carbon atoms, or alkoxyalkyl group of 2 to 4 carbon atoms;

R_3 represents 3-amino-2-pyridyl group ()

wherein, Q is hydrogen atom or straight or branched alkyl group of 1 to 4 carbon atoms), or 2-hydroxyethyl group;

n is an integer of 0 or 1~4;

meantime, the above R_1 that belong to branched hydroxyalkyl group may represent (R)- or (S)-type stereospecificity.

15 Description of the Related Art

About 300 million people around the world are infected with hepatitis caused by Hepatitis B virus (hereinafter referred to as "HBV") as a main pathogen, being accompanied by acute or chronic hepatitis. In severe cases, it is reported that HBV is involved in transforming hepatitis into hepatic cirrhosis hepatocellular carcinoma. In spite of the fact that intensive research have focused on the correlation of liver disease associated with HBV and its molecular biological characteristics, some hepatitis B vaccines and diagnostic reagents have been developed but any effective drug for treating hepatitis B does not exist. Recently, results of some studies have indicated that some nucleoside compounds such as Lamivudine and Famvir, which have been known for AIDS or herpes zoster, are effective in suppressing the proliferation of HBV. However, it has been well known that further development of nucleoside compounds are restricted because of high treatment cost, adverse

reaction, and toxicity.

Under such circumstances, there is an urgent need for the development of effective hepatitis B drug as non-nucleoside compound and in parallel with this trend, some patents related to quinolone compound
5 [European Patent Publication Nos. 563732 and 563734] and iridoids compound [Korean Patent Unexamined Publication No. 94-1886] have been reported to have anti-HBV activities but with no significant development progress has been noticeable.

Meantime, the present applicant has filed patent application related to
10 novel terephthalamide derivatives with antiviral activities as a non-nucleoside compound [Korean Pat. Appln. Nos. 96-72384 and 97-36589].

SUMMARY OF THE INVENTION

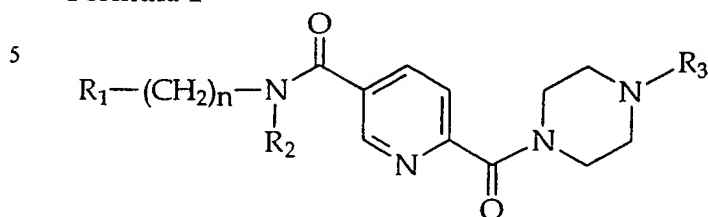
The novel 2,5-pyridinedicarboxylic acid derivatives of the present
15 invention have unique chemical structure as non-nucleoside compounds, and show the anti-viral activities against HBV as well as human immunodeficiency virus (hereinafter referred to as "HIV"). Although HBV is different from HIV, they have the same replication processes, which are the reverse transcription from viral RNA and the digestion of RNA part of RNA-DNA hybrid
20 intermediates. Since the novel 2,5-pyridinedicarboxylic acid derivatives according to the present invention of the formula 1 have mechanism to inhibit reverse transcription, it can be developed as anti-HBV or anti-HIV agents.

Therefore, an object of the present invention is to provide novel 2,5-pyridinedicarboxylic acid derivatives and its pharmaceutically acceptable salts
25 which suppress very effectively the proliferation of various viruses such as HBV and HIV, including its preparing method.

Detailed Description of the Invention

The present invention is related to novel 2,5-pyridinedicarboxylic acid derivatives of the following formula 1 and its pharmaceutically acceptable salts.

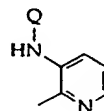
Formula 1



wherein, R₁ represents hydroxy group, straight or branched alkyl group of 1 to 6 carbon atoms, cycloalkyl group of 3 to 6 carbon atoms
 10 unsubstituted or substituted with alkyl group of 1 to 3 carbon atoms, alkyl group of 1 to 3 carbon atoms substituted with cycloalkyl group of 3 to 6 carbon atoms, straight or branched hydroxyalkyl group of 1 to 6 carbon atoms, straight or branched dihydroxyalkyl group of 3 to 6 carbon atoms, straight or branched alkoxy group of 1 to 4 carbon atoms, hydroxyalkoxy group of 2 to 4
 15 carbon atoms, straight or branched alkoxyalkyl group of 2 to 6 carbon atoms, dialkoxyalkyl group of 3 to 6 carbon atoms, dialkylamino group of 2 to 4 carbon atoms, acetylamino group, vinyl group, or saturated or unsaturated five or six membered heterocyclic ring having 1 to 3 hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur; hence, the
 20 heterocycle is unsubstituted or substituted with same or different 1~3 substituents selected from the group consisting of alkyl group of 1 to 3 carbon atoms, alkoxy group of 1 to 3 carbon atoms, hydroxyalkyl group of 1 to 3 carbon atoms, phenyl group, carbamoyl group and hydroxy group;

R₂ represents hydrogen atom, phenyl group, straight or branched alkyl
 25 group of 1 to 4 carbon atoms, straight or branched hydroxyalkyl group of 2 to 4 carbon atoms, or alkoxyalkyl group of 2 to 4 carbon atoms;

R₃ represents 3-amino-2-pyridyl group (



wherein, Q is hydrogen atom or straight or branched alkyl group of 1 to 4 carbon atoms), or 2-hydroxyethyl group;

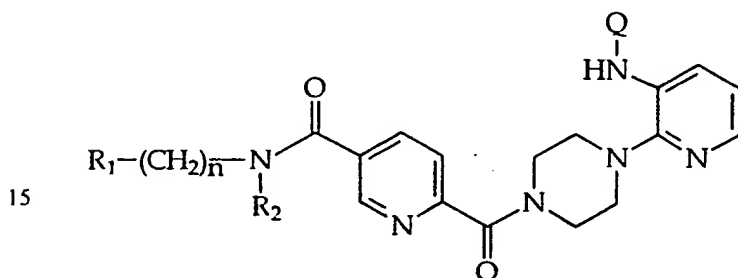
n is an integer of 0 or 1~4;

meantime, the above R₁ that belong to branched hydroxyalkyl group
5 may represent (R)- or (S)-type stereospecificity.

The present invention is explained in more detail as set forth hereunder:

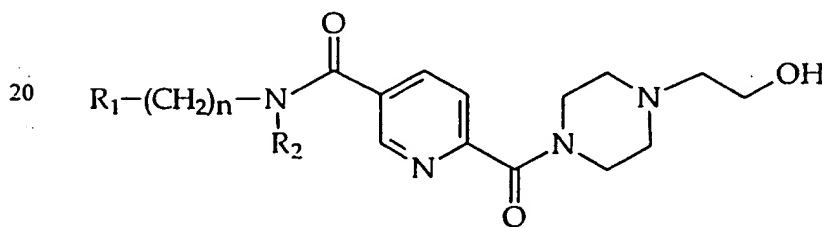
The preferred 2,5-pyridinedicarboxylic acid derivatives of the above
2 formula 1 according to the present invention are represented by the following
10 formula 1a or 1b:

Formula 1a



wherein, R₁, R₂, Q and n are the same as defined above, respectively.

Formula 1b



wherein, R₁, R₂ and n are the same as defined above, respectively.

The more preferred compounds according to the present invention are
25 represented by the formula 1a; wherein R₁, R₂, Q and n are as the follows:

In case where R₁ is hydroxy group, branched hydroxyalkyl group of 3 to 5 carbon atoms, or branched dihydroxyalkyl group of 3 to 5 carbon atoms; R₂ is hydrogen atom, methyl group, ethyl group, 2-hydroxyethyl group or

phenyl group; and n is 0, 2 or 3;

in case where R_1 is straight or branched alkyl group of 2 to 4 carbon atoms, cyclopropyl group, cyclopentyl group, methoxy group, ethoxy group, 2-hydroxyethoxy group, branched alkoxyalkyl group of 4 to 5 carbon atoms, 5 dialkoxyalkyl group of 3 to 5 carbon atoms or dialkylamino group of 2 to 4 carbon atoms; R_2 is hydrogen atom, methyl group, ethyl group, isopropyl group or 2-methoxyethyl group; n is an integer of 0 or 1~3;

in case where R_1 is five or six membered saturated heterocycle selected from the group consisting of dioxolan, tetrahydrofuran, tetrahydrofuranone, 10 tetrahydrothiophenone, pyrrolidinone, morpholine, piperidine and pyrrolidine; R_2 is hydrogen atom, methyl group or ethyl group; n is an integer of 0 or 1~3;

in case where R_1 is five or six membered heteroaryl group selected from the group consisting of pyrazole, isoxazole, thiazole, thiadiazole, 15 imidazole, furan, thiophene, triazole, pyridine, pyrimidine and pyrazine, and in this case, heteroaryl group is unsubstituted or substituted with same or different 1~3 substituents which are selected from the group consisting of methyl group, ethyl group, phenyl group, methoxy group, ethoxy group, carbamoyl group, hydroxy group and hydroxymethyl group; R_2 is hydrogen 20 atom; n is an integer of 0 or 1~3.

In the above cases, Q represents hydrogen atom, ethyl, isopropyl or isobutyl group.

The more preferred compounds of the formula 1b according to the present invention are as follows:

25 R_2 is hydrogen atom; R_1 is straight or branched alkyl group of 2 to 4 carbon atoms or straight or branched alkoxyalkyl group of 2 to 5 carbon atoms; and n is 0.

Further, 2,5-pyridinedicarboxylic acid derivatives of the above formula

1 according to the present invention may form its pharmaceutically acceptable acid-addition salts with acid in accordance with some ordinary methods in the art to which the present invention pertains. For example, acid-addition salts may include inorganic acids such as hydrochloric acid, hydrobromic acid, 5 phosphoric acid and sulfuric acid, or organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, citric acid, maleic acid, succinic acid, fumaric acid, tartaric acid, trifluoroacetic acid, benzoic acid and methanesulfonic acid.

Meantime, 2,5-pyridinedicarboxylic acid derivatives of the above formula 1 according to the present invention may be used as clinically useful 10 anti-hepatitis B and anti-AIDS agents, since it has potent effects against the proliferation of HBV and HIV.

Therefore, the present invention includes pharmaceutical compositions containing 2,5-pyridinedicarboxylic acid derivatives of the above formula 1 and its pharmaceutically acceptable salts as active ingredients.

15 When pharmaceutical compositions of the present invention is intended for clinical application, it may be formulated in to dosage forms containing some exipients commonly used in pharmaceutical field. For example, oral preparations(e.g., tablets, capsules, troches, liquids and suspensions); injectables(e.g., injectable solutions or suspension, or injectable 20 powder which can be immediately use by adding water for injection prior to inject). The pharmaceutical preparations may be administered orally or parenterally(e.g., intravenously, subcutaneously, intraperitoneally or topically).

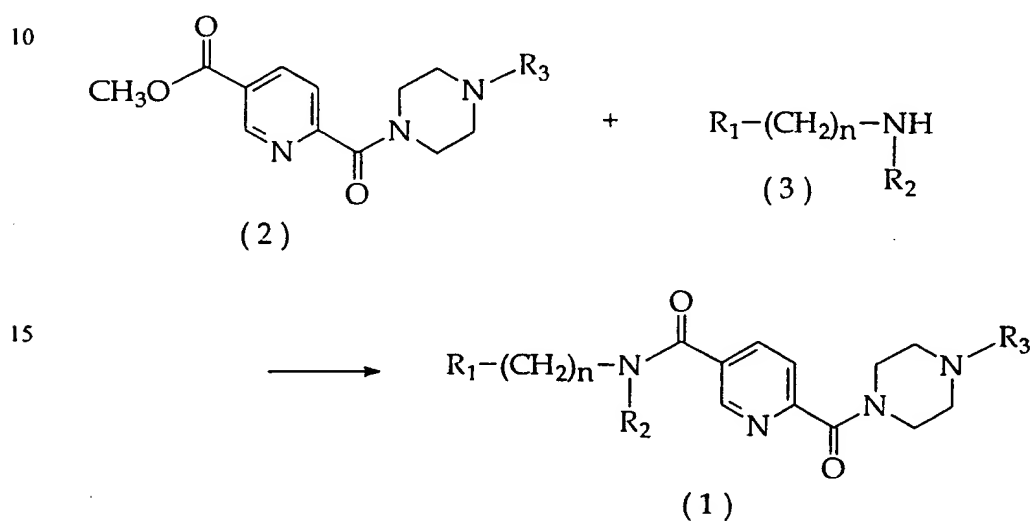
Further the clinical dose of 2,5-pyridinedicarboxylic acid derivatives of the above formula 1 may be appropriately determined range of 10~500 mg, 25 preferably in the range of 50~300 mg. These preparations may be administered at certain intervals of several times(preferably 1-6 times) in accordance with medical or pharmacist's direction.

The present invention also includes a process of preparing 2,5-

pyridinedicarboxylic acid derivatives of the formula 1. The representative process of preparing 2,5-pyridinedicarboxylic acid derivatives of the formula 1 is the following reaction scheme 1.

The following reaction scheme 1 is a process for directly preparing 2,5-pyridinedicarboxylic acid derivatives of the formula 1 by reacting nicotinic acid ester derivatives of the following formula 2 and amine compounds of the following formula 3.

Scheme 1



wherein, R_1 , R_2 , R_3 and n are the same as defined above, respectively.

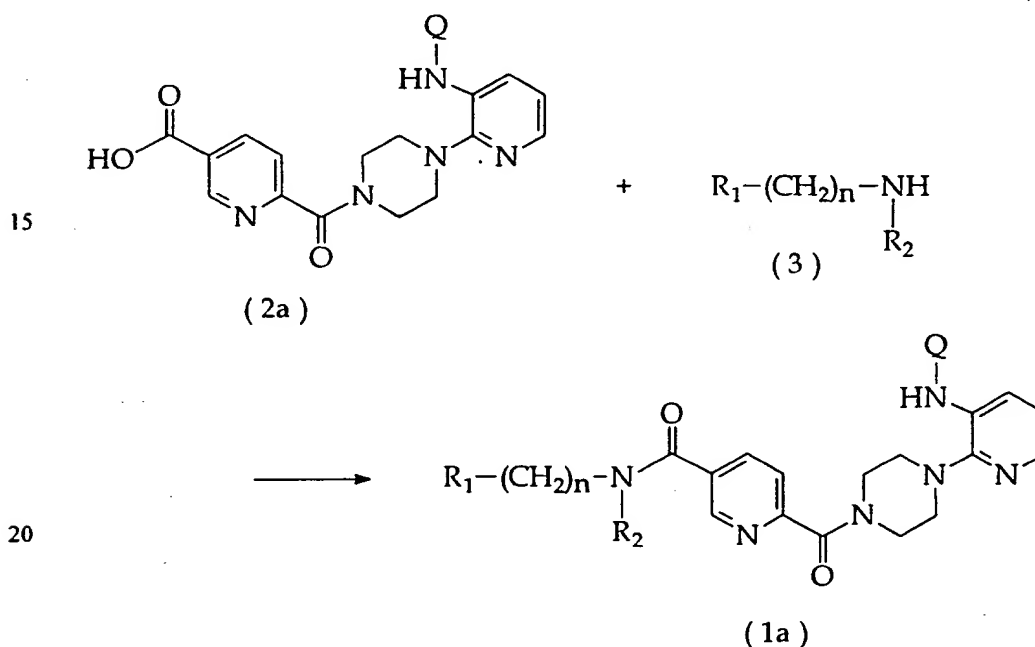
20 According to the reaction scheme 1, The reaction is carried out under direct nucleophilic substitution between amine compounds of the formula 3 and methyl ester group of nicotinic acid ester derivatives of the formula 2. The nucleophilic substitution reaction requires more vigorous reaction condition, since the reactivity of the ester group is relatively lower than that of acid anhydride derivative or acid chloride derivative used in the following Scheme 2. The nucleophilic substitution reaction is completed at 40~90°C within 20 hours in the presence of alcohol solvents (e.g., methanol, ethanol, propanol, isopropanol or butanol) or organic solvents (e.g., acetonitrile, *N,N*-

dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, chloroform, tetrahydrofuran, dioxane or dioxolane).

In particular, 2,5-pyridinedicarboxylic acid derivatives of the formula 1 (wherein, R_3 is 3-amino-2-pyridyl group) can be prepared by the following reaction scheme 2 or 3.

The following reaction scheme 2 is a schematic diagram showing a process of preparing 2,5-pyridinedicarboxylic acid derivatives of the formula 1a as desired compounds (wherein, R_3 is a 3-amino-2-pyridyl group) by reacting of the formula 2a, reactive intermediate of nicotinic acid derivative and amine compounds of the formula 3:

Scheme 2



wherein, R_1 , R_2 and Q are the same as defined above, respectively.

The process for preparing 2,5-pyridinedicarboxylic acid derivatives of the present invention according to the scheme 2 is explained in more detail as set forth hereunder.

First, nicotinic acid derivatives of the formula 2a are reacted with acid chloride compound such as pivaloyl chloride to form acid anhydride

derivatives with good reactivity, or reacted with thionyl chloride to form acid chloride derivatives with high reactivity; then, the intermediates are reacted with amine compounds of the formula 3 to obtain 2,5-pyridinedicarboxylic acid derivatives of the above formula 1a as desired products.

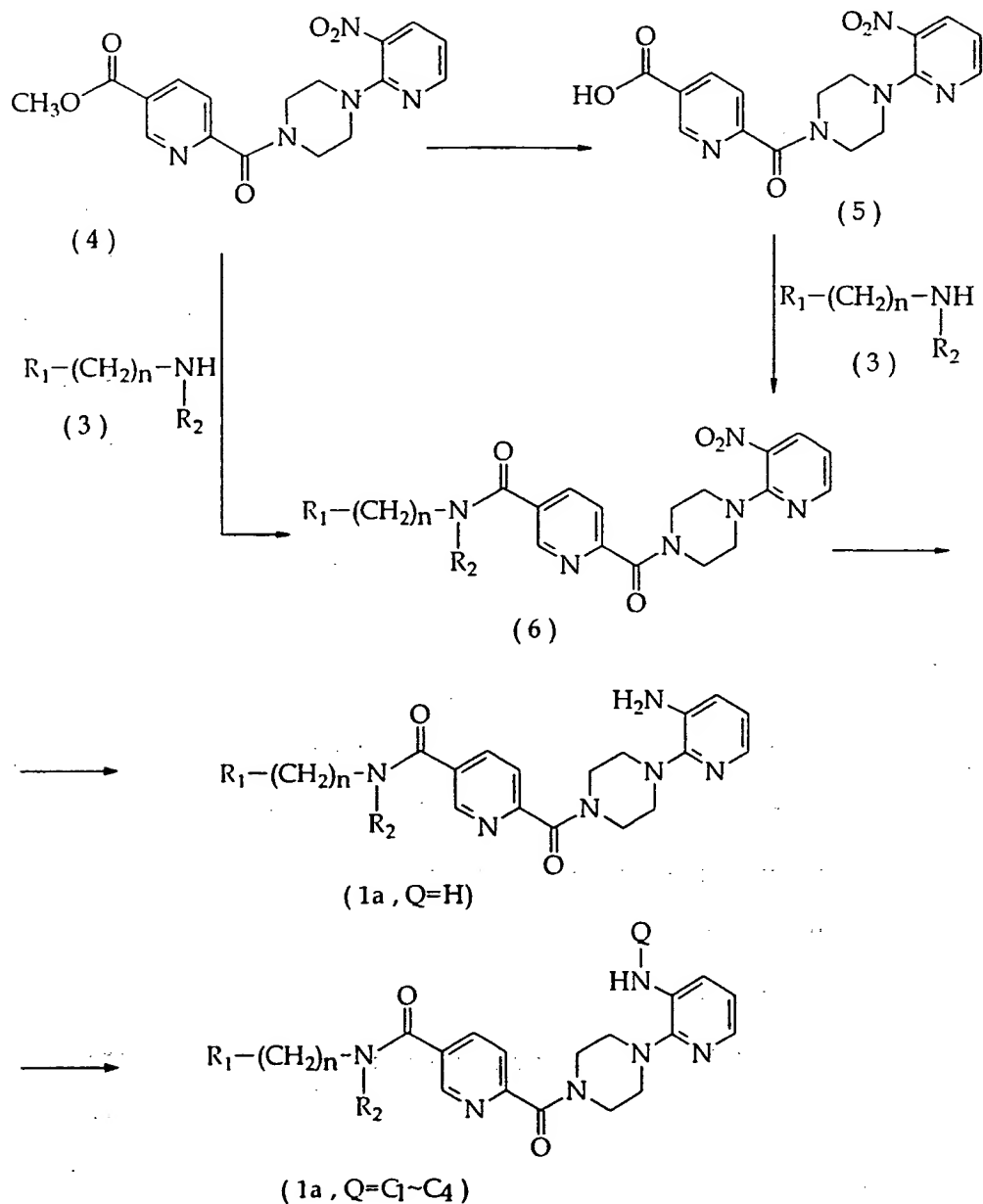
5 These reactions may be performed in the presence of general tertiary organic bases (e.g., triethylamine, *N,N*-diisopropylethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine, *N,N*-dimethylaniline, 2,6-lutidine or pyridine) using 1~1.5 equivalent of amine compounds of the formula 3, or using excess of amine compounds of the
10 formula 3 in the absence of tertiary organic base.

Otherwise, 2,5-pyridinedicarboxylic acid derivatives of the formula 1a as desired products may be also prepared as follows: nicotinic acid derivatives of the Formula 2a are reacted with 1-hydroxybenzotriazole(HOBT) in the presence of 1,3-dicyclohexylcarbodiimide(DCC) to form active ester with good
15 reactivity, and are reacted with amine compounds of the formula 3. This reaction is completed at 5°C ~40°C within 8 hours. In these reactions, it is preferred to use a single solvent or a co-solvent selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran, dioxane, dioxolane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidone.

20 Another process of preparing 2,5-pyridinedicarboxylic acid derivatives (wherein, R_3 is a 3-amino-2-pyridyl group) as desired products of the present invention is illustrated in the following reaction scheme 3.

The following reaction scheme 3 relates to a process, wherein nicotinic acid ester derivatives containing a nitropyridyl group of the following formula
25 4 or nicotinic acid derivatives of the following formula 5 are reacted with amine compounds of the following formula 3 to give intermediates of the following formula 6, and then, the intermediates are further reduced.

Scheme 3



wherein R₁, R₂, Q and n are the same as defined above, respectively.

The process of preparing 2,5-pyridinedicarboxylic acid derivatives of the present invention according to the reaction scheme 3 is explained in more detail as set forth hereunder.

The nicotinic acid derivatives are obtained by hydrolysis of nicotinic acid ester derivatives of the formula 4. In this reaction, a co-solvent containing lower alcohol (e.g., methanol, ethanol or isopropanol) and water is used. The

hydrolysis is completed at less than 40°C within 3 hours in the presence of strong alkali such as sodium hydroxide or potassium hydroxide. The nicotinic acid derivatives of the formula 5, so obtained, are reacted with acid chloride compound such as pivaloyl chloride to form acid anhydride derivatives with good reactivity, or reacted with thionyl chloride to form acid chloride derivatives with high reactivity; then, the intermediates are reacted with amine compounds of the formula 3 to obtain compounds of the formula 6. These reactions are completed at 0°C ~ 30°C within 6 hours in the presence of general tertiary organic bases (e.g., triethylamine, *N,N*-diisopropylethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine, *N,N*-dimethylaniline, 2,6-lutidine or pyridine).

Otherwise, nicotinic acid derivatives of the formula 5 are reacted with 1-hydroxybenzotriazole(HOBT) in the presence of 1,3-dicyclohexylcarbodiimide(DCC) to form active ester with good reactivity, and is reacted with amine compounds of the formula 3 to obtain compounds of the formula 6. This reaction is completed at 5°C ~ 40°C within 8 hours. In these reactions to prepare compounds of the formula 6, it is preferred to use a single solvent or a co-solvent selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran, dioxane, dioxolane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidone.

Further, another process for preparing compounds of the formula 6 is the direct reaction between nicotinic acid ester derivatives of the formula 4, the precursor of the nicotinic acid derivatives of the formula 5 in reaction scheme 3, and amine compounds of the formula 3. This process has an advantage to shorten one step in the manufacturing process. This reaction is carried out under direct nucleophilic substitution between amine compounds of the formula 3 and methyl ester group of nicotinic acid ester derivatives of the formula 4. The nucleophilic substitution reaction requires more stronger

reaction condition, since the reactivity of the ester group is relatively lower than that of the activated acid derivatives of the formula 4. The nucleophilic substitution reaction is completed at 40~90°C within 20 hours in the presence of alcohol solvents (e.g., methanol, ethanol, propanol, isopropanol or butanol) or organic solvents (e.g., acetonitrile, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, chloroform, tetrahydrofuran, dioxane or dioxolane).

The compounds of the formula 6 are reduced by catalytic hydrogenation to give compounds of the Formula 1a (Q: hydrogen atom). Such reduction may be well carried out under high-pressure condition using hydrogen gas in the presence of small amounts of activated metal catalysts such as Raney-nickel or palladium on activated carbon, being widely used in the reductive reaction. Various solvents such as methanol, ethanol, methylene chloride, chloroform or ethyl acetate may be used in this reaction.

Further, the compounds (Q: hydrogen atom) of the formula 1a, so obtained, are under reductive alkylation with acetaldehyde, acetone or isobutyraldehyde in the presence of selective reducing agents such as sodium cyanoborohydride under acidic conditions to form desired products of the formula 1a (Q: straight or branched alkyl group of 1 to 4 carbon atoms). This reaction may be carried out in the presence of organic acid such as acetic acid. Usually, lower alcohol solvents such as methanol or ethanol are used.

The amine compounds of the formula 3, used in reaction schemes 1, 2 and 3 are reagents intended for introducing the substituents R₁ and R₂ into 2,5-pyridinedicarboxylic acid derivatives of the formula 1 as desired products. A person having ordinary skill in the art to which the present invention pertains may easily use some appropriate amine compounds, selected by required substitutes.

Meantime, nicotinic acid derivatives of the formula 2a and nicotinic

acid ester derivatives of the formula 2b used as each starting material in the reaction schemes 1 and 2 associated with the process of preparing 2,5-pyridinedicarboxylic acid derivatives of the formula 1, respectively, can be prepared by the following reaction schemes 4 or 5, prior to use.

5 The following reaction scheme 4 illustrates the process of preparing each compound of the formula 2b and formula 2a, respectively, using 5-(methoxycarbonyl)-2-pyridinecarboxylic acid of the following formula 7 and 1-(3-nitro-2-pyridyl)piperazine of the following formula 8 as starting materials.

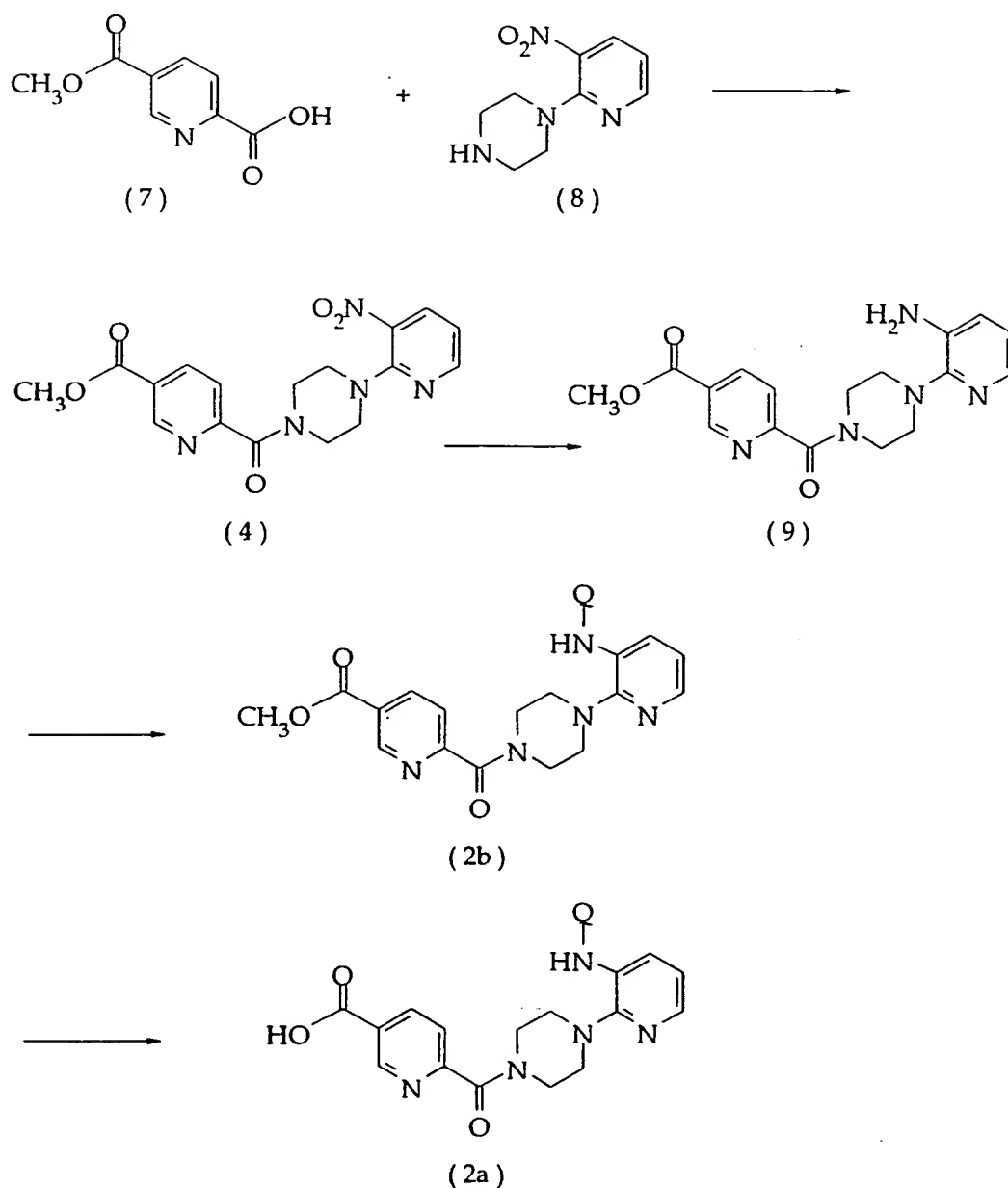
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20

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Scheme 4



wherein Q is the same as defined above.

5-(Methoxycarbonyl)-2-pyridinecarboxylic acid of the formula 7 as a
starting material in reaction scheme 4 may be easily prepared by known
process [Nippon Kagaku Kaishi 1967, Vol. 88, 553~556] from 2,5-
pyridinedicarboxylic acid (= isocinchomeric acid) which can be purchased

for very cheap price. Also, 1-(3-nitro-2-pyridyl)piperazine of the following formula 8 in reaction scheme 4 may be easily prepared by well known process [J. Med. Chem., 1994, Vol. 37, 999~1014] from 2-chloro-3-nitropyridine and piperazine. The process for preparing this starting material is explained in
5 detail in the preparation examples of specifications concerning novel terephthalamide derivatives, which has been disclosed in two patents already filed in Korea by the inventor et al. [Korean Pat. Appln. Nos. 96-72384 and 97-36589].

According to the reaction scheme 4, 5-(methoxycarbonyl)-2-
10 pyridinecarboxylic acid of the formula 7 is reacted with acid chloride compound such as pivaloyl chloride to form acid anhydride derivative with good reactivity; then, the intermediate is reacted with 1-(3-nitro-2-pyridyl)piperazine of the formula 8 to obtain nitcotinic acid ester derivative containing a nitropyridyl group of the formula 4. This reaction is completed at
15 0°C ~ 30°C within 6 hours in the presence of general tertiary organic bases (e.g., triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpiperidine, 4-dimethylaminopyridine, N,N-dimethylaniline, 2,6-lutidine or pyridine). It is preferred to use a single solvent or a co-solvent selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran, dioxane,
20 dioxolane, N,N-dimethylformamide, N,N-dimethylacetamide and N-methylpyrrolidone, etc..

The compound of the formula 4 so obtained, is reduced to form derivative containing aminopyridyl group of the formula 9.

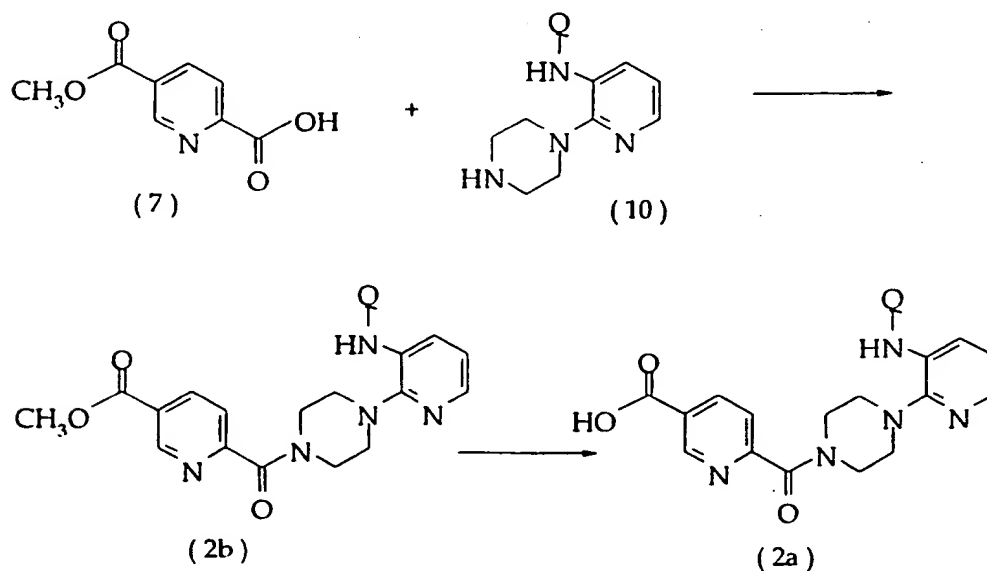
Such reduction is well carried out under high-pressure condition using
25 hydrogen gas in the presence of small amounts of activated metal catalysts such as Raney-nickel or palladium on activated carbon, being widely used in the reductive reaction. Various solvents such as methanol, ethanol, methylene chloride, chloroform or ethyl acetate may be used in this reaction.

Further, derivative containing aminopyridyl group of the formula 9, so obtained, is under reductive alkylation with acetaldehyde, acetone or isobutyraldehyde in the presence of selective reducing agents such as sodium cyanoborohydride under acidic condition to form nicotinic acid ester derivatives containing alkylaminopyridyl group of the formula 2b. Such reaction may be carried out well in the presence of some organic acid such as acetic acid. Usually, lower alcoholic solvents such as methanol or ethanol are used.

The nicotinic acid derivatives of 2a are obtained by hydrolysis of nicotinic acid ester derivatives of the formula 2b. In this reaction, a co-solvent containing lower alcohol (e.g., methanol, ethanol or isopropanol) and water is used. The hydrolysis is completed at below 40°C within 3 hours.

The following reaction scheme 5 illustrates the process of preparing each compound of the formula 2b and formula 2a, respectively, using 5- (methoxycarbonyl)-2-pyridinecarboxylic acid of the following formula 7 and 1-[3-(alkylamino)-2-pyridyl]piperazine of the following formula 10 as starting materials.

Scheme 5



wherein, Q is the same as defined above.

The compound of the formula 7 as a starting material in reaction scheme 5 may be prepared in accordance with Scheme 4. Also, 1-[3-(alkylamino)-2-pyridyl]piperazine of the formula 10 as another starting material in reaction scheme 5 may be prepared by known 4-step processes [*J. Med. Chem.*, 1994, Vol. 37, 999~1014] from 1-(3-nitro-2-pyridyl)piperazine of the formula 8, as described in reaction scheme 4. The process for preparing these starting materials are explained in detail in the preparation examples of specifications concerning novel terephthalamide derivatives, which has been disclosed in the patent disclosure already filed in Korea by the inventor et al. [Korean Pat. Appln. No. 96-72384].

According to the reaction scheme 5, 5-(methoxycarbonyl)-2-pyridinecarboxylic acid of the formula 7 is reacted with some acid chloride compound such as pivaloyl chloride to form acid anhydride derivative with good reactivity; then, the intermediate is reacted with 1-[3-(alkylamino)-2-pyridyl]piperazine of the formula 10 to obtain a compound of the formula 2b. This reactions is completed at 0°C ~ 30°C within 6 hours in the presence of general tertiary organic bases (e.g., triethylamine, *N,N*-diisopropylethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-dimethylaminopyridine, *N,N*-dimethylaniline, 2,6-lutidine or pyridine). In this reaction, it is preferred to use a single solvent or a co-solvent selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran, dioxane, dioxolane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidone.

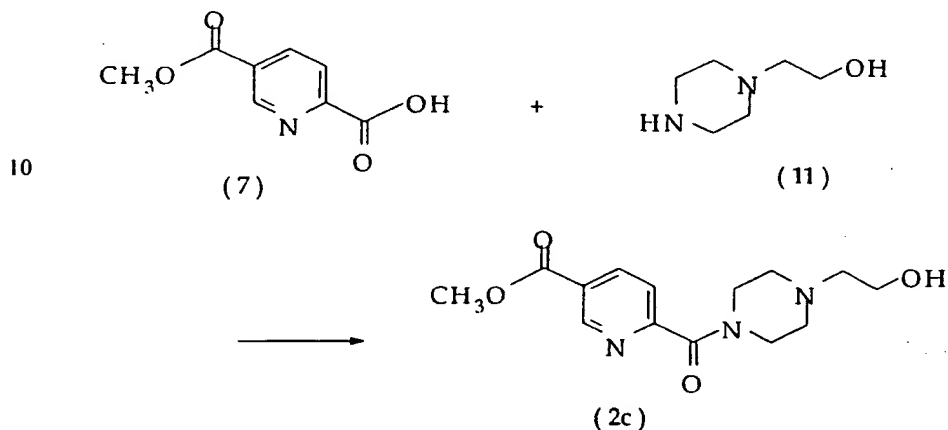
The nicotinic acid ester derivatives of the formula 2b, so obtained, is hydrolyzed in accordance with reaction scheme 4 to obtain nicotinic acid derivatives of the formula 2a.

Meantime, the nicotinic acid ester derivative of the formula 2c used as a starting material in the reaction scheme 1 can be prepared by the following

reaction scheme 6.

The following reaction scheme 6 illustrates the process for preparing 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester of the formula 2c by the reaction between 5-(methoxycarbonyl)-2-pyridinecarboxylic acid of the following formula 7 and 1-(2-hydroxyethyl)piperazine of the following formula 11.

Scheme 6



15 The compound of the formula 7 as a starting material in the reaction scheme 6 may be prepared in accordance with reaction scheme 4. Also, 1-(2-hydroxyethyl)piperazine of the formula 11 as another starting material in reaction scheme 6 may be easily purchased as commercial reagent.

20 The process described in reaction scheme 6 is explained in more detail as set forth hereunder.

5-(Methoxycarbonyl)-2-pyridinecarboxylic acid of the formula 7 is reacted with acid chloride compound such as pivaloyl chloride to form acid anhydride derivative with good reactivity; then, is reacted with 1-(2-hydroxyethyl)piperazine of the formula 11 to obtain 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester of the formula 2c. This reaction is completed at $0^\circ\text{C} \sim 30^\circ\text{C}$ within 6 hours in the presence of general tertiary organic bases (e.g., triethylamine, *N,N*-diisopropylethylamine, *N*-methylmorpholine, *N*-methylpiperidine, 4-

dimethylaminopyridine, *N,N*-dimethylaniline, 2,6-lutidine or pyridine).

Otherwise, 5-(methoxycarbonyl)-2-pyridinecarboxylic acid of the formula 7 is reacted with 1-hydroxybenzotriazole(HOBT) in the presence of 1,3-dicyclohexylcarbodiimide(DCC) to form active ester with good reactivity; then, is reacted with 1-(2-hydroxyethyl)piperazine of the formula 11 to obtain 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester of the formula 2c. This reaction is completed at 5°C ~ 40°C within 8 hours. It is preferred to use a single solvent or co-solvents selected from chloroform, methylene chloride, acetonitrile, tetrahydrofuran, dioxane, dioxolane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and *N*-methylpyrrolidone, etc..

As described above, this invention is explained based on the following examples including preparation examples in more detail but is not limited by these examples.

Preparation example 1: Preparation of 6-[1-(3-nitro-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester

5-(Methoxycarbonyl)-2-pyridinecarboxylic acid(20 g) was added in methylene chloride(200ml), and then, dissolved with the addition of triethylamine(17 ml). The mixture was cooled, pivaloyl chloride(14.5 ml) was added at 0°C ~ 5°C and stirred at 5°C for 2 hours. 1-(3-Nitro-2-pyridyl)piperazine(23 g) and triethylamine(18 ml) were added to the solution in order and the mixture was reacted at 5°C ~ 10°C for 2 hours. The reaction mixture was washed with aqueous sodium bicarbonate and water each twice and then, the separated organic layer was concentrated under reduced pressure. The concentrated residue was treated with ethanol for crystallization and water was added, then the precipitate was filtered. The crude product was recrystallized with ethanol and ether, filtered and dried to give a desired compound of 35.3 g (yield: 86%).

m.p. : 129~130°C

¹H-NMR(CDCl₃), ppm : δ 3.47(m, 2H), 3.61(m, 2H), 3.75(m, 2H), 3.96(m, 5H), 6.83(m, 1H), 7.78(m, 1H), 8.18(m, 1H), 8.35(m, 1H), 8.41(m, 1H), 9.16(m, 1H)

5 **Preparation example 2 : Preparation of 6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester**

6-[1-(3-Nitro-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(6 g) obtained from preparation example 1 was dissolved in methanol(120ml) about 1 ml of Raney-nickel(50% slurry in water) was added
10 and the mixture was filled with hydrogen gas and reduced at 50~60 psi for 4 hours. After completion of the reaction, reaction mixture was filtered through celite and concentrated under reduced pressure. Isopropanol(40 ml) was added to the concentrated residue, stirred, filtered, washed and dried to give a desired compound of 4.97 g (yield: 90%).

15 m.p. : 175~177°C

¹H-NMR(CDCl₃), ppm : δ 3.12(m, 2H), 3.21(m, 2H), 3.67(m, 2H), 3.81(m, 2H), 3.96(m, 5H), 6.84(m, 1H), 6.94(m, 1H), 7.76(m, 2H), 8.37(m, 1H), 9.16(m, 1H)

20 **Preparation example 3 : Preparation of 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester**

Method 1

6-[1-(3-Amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(4 g), so obtained from preparation example 2, was added to methanol(80 ml) and with the successive addition of acetone(2 ml), acetic acid(5 ml) and
25 sodium cyanoborohydride(2.5 g) at 10°C. The mixture was stirred at room temperature for 3 hours. Aqueous 3N-sodium hydroxide was added to the mixture for neutralization (pH = ~7.5), followed by the slow addition of excess of water for precipitation. After 2-hours stirring, the precipitate was filtered,

washed with water and isopropanol, and dried to give a desired compound of 3.73 g(yield: 83%).

Method 2

5 5-(Methoxycarbonyl)-2-pyridinecarboxylic acid(5g) was added in methylene chloride(70 ml) and then dissolved with the addition of triethylamine(4.3ml). The mixture was cooled, pivaloyl chloride(3.6 ml) was added at 0°C ~5°C, and the mixture was stirred at 5°C for 2 hours. Then, 1-[3-(isopropylamino)-2-pyridyl]piperazine(5.8 g) and triethylamine(4.5 ml) were
10 added to the solution, and the mixture was stirred at 5°C ~10°C for 2 hours. The reaction solution was washed with aqueous sodium bicarbonate and water twice and then, separated organic layer was concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization, stirred and filtered. The residue was recrystallized with isopropanol, filtered
15 and dried to give a desired compound of 7.87 g (yield: 78%).

m.p. : 93 ~ 94°C

¹H-NMR(CDCl₃), ppm : δ 1.21(d, 6H), 3.09(m, 2H), 3.16(m, 2H), 3.52(m, 1H), 3.69(m, 2H), 3.95(m, 5H), 4.13(m, 1H), 6.82(m, 1H), 6.92(m, 1H), 7.71(m, 2H), 8.39(m, 1H), 9.17(m, 1H)

20

Preparation example 4 : Preparation of 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester

6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(5 g) was added to methanol(100 ml) and with the addition of acetic
25 acid(4 ml) and acetaldehyde(1.2 ml) at 5°C ~10°C, the mixture was stirred for 30 minutes. With the addition of sodium cyanoborohydride(1 g), the mixture was stirred at 15°C for 2 hours. Sodium cyanoborohydride(1 g) was added again, and the mixture was further stirred for 1 hour. Water (50 ml) and 3N-

sodium hydroxide solution were added to the mixture for neutralization (pH 7.5) and then, methanol was concentrated under reduced pressure. After the mixture was extracted with chloroform, the separated organic layer was concentrated under reduced pressure. The residue was treated with ether for
5 crystallization and recrystallized with ethyl acetate and hexane. The product was filtered and dried to give a desired compound of 4.1 g (yield: 76%).

m.p. : 80 ~ 81 °C

¹H-NMR(CDCl₃), ppm : δ 1.29(t, 3H), 3.13(m, 4H), 3.20(m, 2H), 3.70(m, 2H),
3.96(m, 5H), 4.17(m, 1H), 6.87(m, 1H), 6.95(m, 1H), 7.72(m, 2H), 8.38(m, 1H),
10 9.17(m, 1H)

Preparation example 5: Preparation of 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester

By the same procedure as described in the preparation example 4,
15 synthesis was carried out starting with 6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using isobutyraldehyde. Then, the product was recrystallized with ethanol and hexane to give a desired compound.

Yield: 71%

20 m.p. : 82 ~ 84 °C

¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.90(m, 1H), 2.87(m, 2H), 3.07(m, 2H),
3.16(m, 2H), 3.68(m, 2H), 3.91(m, 5H), 4.32(s, 1H), 6.79(m, 1H), 6.90(m, 1H),
7.66(m, 1H), 7.71(m, 1H), 8.38(m, 1H), 9.17(s, 1H)

25 Preparation example 6 : Preparation of 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid

6-[1-[3-(Isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester(3 g) was dissolved in methanol(30 ml) and with the addition

of aqueous 1N sodium hydroxide (16 ml), the mixture was hydrolyzed at 25°C for 2 hours. 2N hydrochloric acid was slowly added to the mixture for neutralization (pH = ~5), followed by the slow addition of excess of water to precipitate. After 2-hours stirring, the precipitate was filtered, washed with water and dried to give a desired compound of 2.63 g(yield: 91%).

m.p. : 211 ~ 214 °C

¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 3.16(m, 2H), 3.36(m, 2H), 3.57(m, 1H), 3.70(m, 2H), 3.96(m, 2H), 6.96(m, 1H), 7.07(m, 1H), 7.79(m, 1H), 8.00(m, 1H), 8.50(m, 1H), 9.31(m, 1H)

Preparation example 7 : Preparation of 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid

6-[1-[3-(Ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester(3 g) was dissolved in methanol(18 ml) and with the addition of aqueous 1N-sodium hydroxide (18 ml), the mixture was hydrolyzed at 30°C for 2 hours. 3N-hydrochloric acid was slowly added to the mixture for neutralization (pH = 5~6), followed by the addition of isopropanol(25 ml) and the slow addition of excess of water to precipitate. After 2-hours stirring at 20°C, the precipitate was filtered, washed with water and dried to give a desired compound of 2.48 g(yield: 86%).

m.p. : 155 ~ 157 °C

¹H-NMR(DMSO-*d*₆), ppm : δ 1.17(t, 3H), 2.84(m, 2H), 2.98(m, 4H), 3.52(m, 2H), 3.86(m, 2H), 6.94(m, 2H), 7.54(m, 1H), 7.71(m, 1H), 8.38(m, 1H), 9.06(m, 1H), 13.58(s, 1H)

Preparation example 8 : Preparation of 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid

By the same procedure as described in the preparation example 7,

synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester..

Yield: 92%

m.p. : 160~163 °C

5 ¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.92(m, 1H), 2.92(m, 2H), 3.18(m, 2H), 3.33(m, 2H), 3.70(m, 2H), 3.96(m, 2H), 6.92(m, 1H), 7.03(m, 1H), 7.75(m, 1H), 7.98(m, 1H), 8.49(m, 1H), 9.31(s, 1H)

Preparation example 9 : Preparation of 6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid

6-[1-(3-Amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(3 g) was dissolved in methanol(25 ml) and with the addition of aqueous 1N-sodium hydroxide (20 ml), the mixture was stirred at 25 °C for 2 hours. With the slow addition of 3N-hydrochloric acid for neutralization (pH = ~5),
15 water (25 ml) was slowly added to the mixture for precipitate. After a 1-hour stirring, the precipitate was filtered, washed with water and dried to give a desired compound of 2.53 g(yield: 88%).

m.p. : 137~140 °C

¹H-NMR(TFA-d₁), ppm : δ 3.68(m, 4H), 4.08(m, 2H), 4.31(m, 2H), 7.45(m, 1H),
20 7.81(m, 2H), 8.54(m, 1H), 9.41(m, 1H), 9.67(m, 1H)

Preparation example 10 : Preparation of 6-[1-(3-nitro-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid

6-[1-(3-Nitro-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(10 g) was dissolved in methanol(75 ml) and with the addition of aqueous 1N-sodium hydroxide (75 ml), the mixture was stirred at 30 °C for 2 hours. With the slow addition of 3N-hydrochloric acid for neutralization (pH = ~5),
25 water (110 ml) was slowly added to the mixture for precipitate. After 2-hours

stirring, the precipitate was filtered, washed with water and dried to give a desired compound of 8.66 g(yield: 90%).

m.p. : 185~187°C

¹H-NMR(DMSO-*d*₆), ppm : δ 3.37(m, 2H), 3.52(m, 4H), 3.78(m, 2H), 6.94(m, 1H), 7.75(m, 1H), 8.28(m, 1H), 8.39(m, 2H), 9.06(m, 1H), 13.61(s, 1H)

Preparation example 11: Preparation of 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester

Method 1:

5-(Methoxycarbonyl)-2-pyridinecarboxylic acid(50 g) was added to methylene chloride(550 ml) and with the addition of triethylamine(42.5 ml), the mixture was dissolved. After being cooled, pivaloyl chloride(36 ml) was added to the mixture at 0°C ~ 5°C and stirred at 5°C for 2 hours. The mixture of 1-(2-hydroxyethyl)piperazine(37 g) and *N,N*-diisopropylethylamine(48 ml) were added to the mixture at 5°C and the mixture was reacted at 5°C ~ 10°C for 2 hours. The solution was washed with aqueous sodium bicarbonate and water twice. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization and recrystallized with ethyl acetate and isopropyl ether to give a desired compound of 57.5 g (yield: 71%).

m.p. : 95~96°C

¹H-NMR(CDCl₃), ppm : δ 2.65(m, 4H), 2.72(m, 2H), 3.67(m, 4H), 3.77(m, 2H), 3.96(s, 3H), 7.72(d, 1H), 8.38(m, 1H), 9.16(d, 1H)

Method 2:

5-(Methoxycarbonyl)-2-pyridinecarboxylic acid(5 g) was added to a co-solvent of tetrahydrofuran(40 ml) and methylene chloride(60 ml) and with the successive addition of 1,3-dicyclohexylcarbodiimide(11.5 g) and 1-

hydroxybenzotriazole(4.1 g) at 15°C ~ 20°C, the mixture was reacted for 2 hours. After being cooled, 1-(2-hydroxyethyl)piperazine(3.8 g) was added to the mixture at 10°C and stirred at the same temperature for 2 hours. The reaction mixture was heated and further stirred at 20°C ~ 25°C for 30 minutes. With the
5 addition of methylene chloride(90 ml), the mixture was washed with water three times, dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization and recrystallized with ethyl acetate and tetrahydrofuran to give a desired compound of 6.3 g (yield: 78%).

10 m.p. : 95 ~ 96°C

¹H-NMR(CDCl₃), ppm : δ 2.65(m, 4H), 2.72(m, 2H), 3.67(m, 4H), 3.77(m, 2H), 3.96(s, 3H), 7.72(d, 1H), 8.38(m, 1H), 9.16(d, 1H)

Example 1 : 5-[N-(2-hydroxyethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine
15

Triethylamine(0.54 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazine-4-yl-carbonyl]nicotinic acid(1.3 g) in methylene chloride(40 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.45 ml) at 0°C ~ 5°C, the reaction mixture was stirred at 5°C for 2
20 hours. With the addition of triethylamine(0.6 ml) and ethanolamine(0.25 ml), the mixture was stirred at 5°C ~ 10°C for 3 hours. The solution was washed with aqueous sodium bicarbonate and water twice. The separated organic layer was concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization and recrystallized with ethanol and
25 isopropyl ether to give a desired compound of 1.2 g (yield: 83%).

m.p. : 163 ~ 165°C

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 3.08(m, 2H), 3.18(m, 2H), 3.63(m, 5H), 3.84(m, 2H), 3.93(m, 2H), 4.13(m, 1H), 6.85(m, 1H), 6.96(m, 1H), 7.48-7.65(m,

3H), 8.10(m, 1H), 8.89(m, 1H)

Example 2 : 5-[N-(3-Hydroxypropyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazine-4-yl-carbonyl]pyridine

5 6-[1-[3-(Isopropylamino)-2-pyridyl]piperazine-4-yl-carbonyl]nicotinic acid methyl ester(2.5 g) was dissolved in methanol(40 ml) and with the addition of 3-amino-1-propanol(0.95 g), the mixture was heated to reflux for 12 hours and cooled. The excess of water was added slowly at 25°C for precipitation, the mixture was stirred for 2 hours and filtered. The filtered
10 solid was recrystallized with isopropanol and ether, filtered and dried to give a desired compound of 2.17 g (yield: 78%).

m.p. : 139 ~ 140°C

¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 1.84(m, 2H), 3.08(m, 2H), 3.16(m, 2H), 3.52(m, 1H), 3.62(m, 4H), 3.75(m, 2H), 3.94(m, 2H), 4.13(m, 1H), 6.84(m, 1H),
15 6.94(m, 1H), 7.50(m, 1H), 7.65(m, 2H), 8.13(m, 1H), 8.91(m, 1H)

Example 3 : 5-[N-[(1R)-2-hydroxy-1-methylethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazine-4-yl-carbonyl]pyridine

By the same procedure as described in the example 1, synthesis was
20 carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazine-4-yl-carbonyl]nicotinic acid and using (R)-(-)-2-amino-1-propanol. Then, the product was recrystallized with ethanol and hexane to give a desired compound.

Yield: 80 %

25 m.p. : 129 ~ 130°C

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 1.28(d, 3H), 3.05(m, 2H), 3.21(m, 2H), 3.63(m, 4H), 3.85(m, 2H), 4.01(m, 1H), 4.11(m, 1H), 4.25(m, 1H), 6.83(m, 1H), 6.94(m, 1H), 7.28(m, 1H), 7.41(m, 1H), 7.65(m, 1H), 8.03(m, 1H), 8.85(m, 1H)

Example 4 : 5-[N-[(1S)-2-hydroxy-1-methylethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 3, synthesis was
5 carried out using (S)-(+)-2-amino-1-propanol.

Yield: 76 %

m.p. : 129~130°C

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 1.30(d, 3H), 3.04(m, 2H), 3.20(m, 2H),
3.60(m, 4H), 3.83(m, 2H), 4.01(m, 1H), 4.11(m, 1H), 4.25(m, 1H), 6.82(m, 1H),
10 6.94(m, 1H), 7.31(m, 1H), 7.39(m, 1H), 7.64(m, 1H), 8.04(m, 1H), 8.84(m, 1H)

Example 5 : 5-[N-(2-hydroxy-1-methylethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 3, synthesis was
15 carried out using 2-amino-1-propanol.

Yield: 82 %

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 1.30(d, 3H), 3.05(m, 2H), 3.21(m, 2H),
3.62(m, 4H), 3.84(m, 2H), 4.00(m, 1H), 4.11(m, 1H), 4.26(m, 1H), 6.82(m, 1H),
6.95(m, 1H), 7.30(m, 1H), 7.41(m, 1H), 7.95(m, 1H), 8.03(m, 1H), 8.84(m, 1H)

20

Example 6 : 5-[N-(1,1-dimethyl-2-hydroxyethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 1, synthesis was
carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-
25 carbonyl]nicotinic acid and using 2-amino-2-methyl-1-propanol. Then, the
product was recrystallized with ethyl acetate and ether to give a desired
compound.

Yield: 74 %

m.p. : 145 ~ 146 °C

¹H-NMR(CDCl₃), ppm : δ 1.21(d, 6H), 1.43(d, 6H), 3.08(m, 2H), 3.17(m, 2H), 3.54(m, 1H), 3.63(m, 2H), 3.69(m, 2H), 3.94(m, 2H), 4.14(m, 1H), 6.68(m, 1H), 6.86(m, 1H), 6.94(m, 1H), 7.55(m, 1H), 7.67(m, 1H), 8.09(m, 1H), 8.88(m, 1H)

5

Example 7 : 5-[N-[(1R)-1-ethyl-2-hydroxyethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using (R)-(-)-2-amino-1-butanol. Then, the product was recrystallized with ethanol and petroleum ether to give a desired compound.

Yield: 83 %

m.p. : 85 ~ 88 °C

15 ¹H-NMR(CDCl₃), ppm : δ 0.99(t, 3H), 1.22(d, 6H), 1.68(m, 2H), 3.06(m, 2H), 3.17(m, 2H), 3.52(m, 3H), 3.68(m, 1H), 3.82(m, 2H), 4.01(m, 3H), 6.85(m, 1H), 6.96(m, 1H), 7.30(m, 1H), 7.38(m, 1H), 7.65(m, 1H), 8.03(m, 1H), 8.85(m, 1H)

Example 8 : 5-[N-[(1S)-1-ethyl-2-hydroxyethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

20

By the same procedure as described in the example 7, synthesis was carried out using (S)-(+)-2-amino-1-butanol.

Yield: 81 %

25 ¹H-NMR(CDCl₃), ppm : δ 0.99(t, 3H), 1.21(d, 6H), 1.67(m, 2H), 3.06(m, 2H), 3.17(m, 2H), 3.52(m, 3H), 3.67(m, 1H), 3.81(m, 2H), 4.01(m, 3H), 6.84(m, 1H), 6.96(m, 1H), 7.30(m, 1H), 7.37(m, 1H), 7.65(m, 1H), 8.05(m, 1H), 8.86(m, 1H)

Example 9 : 5-[N-(1-ethyl-2-hydroxyethyl)carbamoyl]-2-[1-[3-

(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 7, synthesis was carried out using 2-amino-1-butanol.

Yield: 77 %

5 ¹H-NMR(CDCl₃), ppm : δ 0.98(t, 3H), 1.22(d, 6H), 1.67(m, 2H), 3.06(m, 2H), 3.16(m, 2H), 3.53(m, 3H), 3.68(m, 1H), 3.82(m, 2H), 4.02(m, 3H), 6.85(m, 1H), 6.97(m, 1H), 7.29(m, 1H), 7.38(m, 1H), 7.65(m, 1H), 8.03(m, 1H), 8.85(m, 1H)

Example 10 : 5-[N-[(1R)-2-hydroxy-1-isopropylethyl]carbamoyl]-2-[1-[3-
10 **(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine**

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using (R)-(-)-2-amino-3-methyl-1-butanol. Then, the product was recrystallized with acetone and hexane to give a desired
15 compound.

Yield: 73 %

¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.22(d, 6H), 2.00(m, 1H), 3.10(m, 4H), 3.50(m, 4H), 3.83(m, 2H), 4.00(m, 3H), 6.82(m, 1H), 6.93(m, 1H), 7.29(m, 1H), 7.40(m, 1H), 7.65(m, 1H), 8.02(m, 1H), 8.85(m, 1H)

20

Example 11 : 5-[N-[(1S)-2-hydroxy-1-isopropylethyl]carbamoyl]-2-[1-[3-
(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 10, synthesis was carried out using (S)-(+)-2-amino-3-methyl-1-butanol.

25 Yield: 75 %

¹H-NMR(CDCl₃), ppm : δ 1.00(d, 6H), 1.23(d, 6H), 2.01(m, 1H), 3.13(m, 4H), 3.52(m, 4H), 3.83(m, 2H), 4.00(m, 3H), 6.83(m, 1H), 6.94(m, 1H), 7.29(m, 1H), 7.39(m, 1H), 7.66(m, 1H), 8.00(m, 1H), 8.85(m, 1H)

Example 12 : 5-[N-(2-hydroxy-1-isopropylethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 10, synthesis was carried out using 2-amino-3-methyl-1-butanol.

Yield: 80 %

¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.23(d, 6H), 2.01(m, 1H), 3.12(m, 4H), 3.52(m, 4H), 3.82(m, 2H), 4.01(m, 3H), 6.82(m, 1H), 6.95(m, 1H), 7.28(m, 1H), 7.39(m, 1H), 7.66(m, 1H), 8.01(m, 1H), 8.84(m, 1H)

10

Example 13 : 5-[N-[Bis(hydroxymethyl)methyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 2, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using 2-amino-1,3-propandiol. Then, the product was recrystallized with ethyl acetate and hexane to give a desired compound.

Yield: 78 %

m.p. : 90 ~ 93 °C

¹H-NMR(CDCl₃), ppm : δ 1.21(d, 6H), 3.07(m, 4H), 3.51(m, 4H), 3.85(m, 6H), 4.16(m, 2H), 6.85(m, 1H), 6.93(m, 1H), 7.48(m, 1H), 7.62(m, 1H), 7.85(m, 1H), 8.13(m, 1H), 8.92(m, 1H)

Example 14 : 5-[N-ethyl-N-(2-hydroxyethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

25

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 2-(ethylamino)ethanol. And then, the

product was recrystallized with isopropanol and hexane to give a desired compound.

Yield: 74 %

m.p. : 134 ~ 135 °C

5 ¹H-NMR(CDCl₃), ppm : δ 1.15(t, 3H), 1.22(d, 6H), 3.14(m, 4H), 3.33(m, 2H), 3.54(m, 1H), 3.71(m, 4H), 3.92(m, 4H), 4.14(m, 1H), 6.85(m, 1H), 6.93(m, 1H), 7.68(m, 2H), 7.84(m, 1H), 8.64(m, 1H)

Example 15 : 5-[N-(2-hydroxyethyl)-N-methylcarbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine
10

By the same procedure as described in the example 14, synthesis was carried out using 2-(methylamino)ethanol.

Yield: 82 %

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 3.02(s, 3H), 3.12(m, 4H), 3.54(m, 1H),
15 3.72(m, 4H), 3.93(m, 4H), 4.13(m, 1H), 6.85(m, 1H), 6.93(m, 1H), 7.68(m, 2H), 7.84(m, 1H), 8.64(m, 1H)

Example 16 : 5-[N,N-bis(2-hydroxyethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine
20

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using diethanolamine. And then, the product was recrystallized with isopropanol and ether to give a desired compound.

Yield: 77 %

25 m.p. : 130 ~ 132 °C

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 3.05(m, 2H), 3.13(m, 2H), 3.55(m, 1H), 3.61(m, 6H), 3.90(m, 2H), 4.05(m, 4H), 4.21(m, 1H), 6.91(m, 1H), 7.02(m, 1H), 7.64(m, 1H), 7.69(m, 1H), 8.20(m, 1H), 8.95(s, 1H)

Example 17 : 5-[N-(2-hydroxyethyl)-N-phenylcarbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using N-phenylethanolamine. And then, the product was recrystallized with isopropylether to give a desired compound.

Yield: 65 %

m.p. : 127~130°C

¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 3.06(m, 2H), 3.14(m, 2H), 3.55(m, 1H), 3.62(m, 2H), 3.88(m, 4H), 4.16(m, 3H), 6.86(m, 1H), 6.95(m, 1H), 7.13(m, 2H), 7.23(m, 1H), 7.30(m, 2H), 7.50(m, 1H), 7.68(m, 1H), 7.74(m, 1H), 8.51(s, 1H)

Example 18 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-hydroxyethyl)carbamoyl]pyridine

By the same procedure as described in the example 2, synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using ethanolamine. And then, the product was recrystallized with ethanol and hexane to give a desired compound.

Yield: 73 %

m.p. : 178~180°C

¹H-NMR(CDCl₃), ppm : δ 1.31(t, 3H), 3.13(m, 4H), 3.21(m, 2H), 3.63(m, 4H), 3.84(m, 2H), 3.96(m, 2H), 4.22(m, 1H), 6.86(m, 1H), 6.96(m, 1H), 7.51(m, 1H), 7.64(m, 1H), 7.69(m, 1H), 8.10(m, 1H), 8.91(s, 1H)

Example 19 : 5-[N-(1,1-dimethyl-2-hydroxyethyl)carbamoyl]-2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 2-amino-2-methyl-1-propanol. And then, the product was recrystallized to give a desired compound.

5 Yield: 70 %

m.p. : 128 ~ 130 °C

¹H-NMR(CDCl₃), ppm : δ 1.30(t, 3H), 1.46(s, 6H), 3.16(m, 4H), 3.23(m, 2H), 3.96(m, 4H), 3.97(m, 2H), 6.70(s, 1H), 6.90(m, 1H), 6.99(m, 1H), 7.61(m, 1H), 7.71(m, 1H), 8.12(m, 1H), 8.91(s, 1H)

10

Example 20 : 2-[1-(3-Amino-2-pyridyl)piperazine-4-yl-carbonyl]-5-[N-(2-hydroxyethyl)carbamoyl]pyridine

6-[1-(3-Amino-2-pyridyl)piperazine-4-yl-carbonyl]nicotinic acid(0.5 g) was added to a co-solvent of tetrahydrofuran(10 ml) and methylene chloride(10 ml) and with the successive addition of 1,3-dicyclohexylcarbodiimide(0.65 g) and 1-hydroxybenzotriazole(0.23 g) at 15 ~ 20 °C, the mixture was stirred for 2 hours. With the addition of ethanolamine(0.18 ml), the mixture was stirred again at 20 ~ 25 °C for 2 hours. Methylene chloride(30 ml) was added again to the mixture, washed with water 3 times, dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization. The solid was recrystallized with ethanol and hexane to give a desired compound of 0.44g (yield : 78%).

20 m.p. : 197 ~ 199 °C

¹H-NMR(CDCl₃+CD₃OD), ppm : δ 3.16(m, 2H), 3.25(m, 2H), 3.59(m, 2H), 3.68(s, 2H), 3.77(m, 2H), 3.98(m, 2H), 6.94(m, 1H), 7.09(m, 1H), 7.74(m, 2H), 8.30(m, 1H), 9.30(s, 1H)

Example 21 : 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-[N-(1,1-dimethyl-2-hydroxyethyl)carbamoyl]pyridine

By the same procedure as described in the example 20, synthesis was carried out using 2-amino-2-methyl-1-propanol.

5 Yield: 67%

m.p. : 120 ~ 122°C

¹H-NMR(CDCl₃), ppm : δ 1.46(s, 6H), 3.16(m, 2H), 3.26(m, 2H), 3.67(m, 2H), 3.71(s, 2H), 3.97(m, 2H), 6.67(s, 1H), 6.89(m, 1H), 7.01(m, 1H), 7.60(m, 1H), 7.79(m, 1H), 8.11(m, 1H), 8.90(s, 1H)

10

Example 22 : 5-[N-(2-hydroxyethyl)carbamoyl]-2-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 1, synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid to give a desired compound.

15

Yield: 80%

m.p. : 136 ~ 139°C

¹H-NMR(CDCl₃), ppm : δ 0.99(d, 6H), 1.90(m, 1H), 2.88(m, 2H), 3.06(m, 2H), 3.18(m, 2H), 3.60(m, 4H), 3.82(m, 2H), 3.94(m, 2H), 4.32(m, 1H), 6.78(m, 1H), 6.91(m, 1H), 7.46(m, 1H), 7.55(m, 1H), 7.65(m, 1H), 8.05(m, 1H), 8.86(s, 1H)

20

Example 23 : 5-[N-(1,1-dimethyl-2-hydroxyethyl)carbamoyl]-2-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 6, synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid to give a desired compound.

25

Yield: 71%

m.p. : 140 ~ 143°C

¹H-NMR(CDCl₃), ppm : δ 0.99(d, 6H), 1.43(s, 6H), 1.90(m, 1H), 2.88(m, 2H), 3.05(m, 2H), 3.17(m, 2H), 3.62(m, 2H), 3.68(s, 2H), 3.94(m, 2H), 4.32(m, 1H), 6.65(s, 1H), 6.79(m, 1H), 6.81(m, 1H), 7.53(m, 1H), 7.65(m, 1H), 8.05(m, 1H), 8.86(s, 1H)

5

Example 24 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-(N-isopropylcarbamoyl)pyridine

Triethylamine(1.6 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(4 g) in methylene chloride(50 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(1.4 ml) at 0°C ~ 5°C, the mixture was stirred at 5°C for 1 hour. With the addition of triethylamine(1.7 ml) and isopropylamine(1.2 ml), the mixture was stirred at 10°C for 2 hours. The solution was washed with aqueous sodium bicarbonate and water twice. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Isopropanol(40 ml) was added to the concentrated residue, stirred and filtered. The solid was recrystallized with ethyl acetate and ether to give a desired compound of 3.6 g (yield: 81%).

15

m.p. : 175 ~ 176°C

¹H-NMR(CDCl₃), ppm : δ 1.21(d, 6H), 1.28(d, 6H), 3.07(m, 2H), 3.15(m, 2H), 3.54(m, 1H), 3.67(m, 2H), 3.94(m, 2H), 4.13(m, 1H), 4.28(m, 1H), 6.33(m, 1H), 6.84(m, 1H), 6.93(m, 1H), 7.65(m, 2H), 8.11(m, 1H), 8.90(m, 1H)

20

Example 25 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-(N-isopropylcarbamoyl)pyridine

25

6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester(2 g) was dissolved in methanol(25 ml) and with the addition of isopropylamine(5 ml), the mixture was heated to reflux for 12 hours. The

mixture was concentrated under reduced pressure to remove the solvent. The residue was treated with ether for crystallization, and the solid was recrystallized with chloroform and hexane to give a desired compound of 1.59 g (yield: 74%).

5 m.p. : 188 ~ 190 °C

¹H-NMR(CDCl₃), ppm : δ 1.29(m, 9H), 3.16(m, 6H), 3.70(m, 2H), 3.97(m, 2H), 4.20(m, 1H), 4.32(m, 1H), 6.27(m, 1H), 6.87(m, 1H), 6.96(m, 1H), 7.71(m, 2H), 8.14(m, 1H), 8.93(m, 1H)

10 **Example 26 : 2-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-(N-isopropylcarbamoyl)pyridine**

By the same procedure as described in the example 24, synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid to give a desired compound.

15 Yield: 76%

m.p. : 132 ~ 134 °C

¹H-NMR(CDCl₃), ppm : δ 1.02(d, 6H), 1.30(d, 6H), 1.93(m, 1H), 2.91(m, 2H), 3.08(m, 2H), 3.19(m, 2H), 3.69(m, 2H), 3.98(m, 2H), 4.31(m, 2H), 6.21(d, 1H), 6.83(m, 1H), 6.93(m, 1H), 7.68(m, 2H), 8.15(m, 1H), 8.93(s, 1H)

20

Example 27 : 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-(N-isopropylcarbamoyl)pyridine

Step (1) : Preparation of 5-(N-isopropylcarbamoyl)-2-[1-(3-nitro-2-
25 pyridyl)piperazin-4-yl-carbonyl]pyridine

Triethylamine(0.85 ml) was added to 6-[1-(3-nitro-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid(2 g) in methylene chloride(25 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.7 ml) at 0 °C ~ 5 °C,

the mixture was stirred at 5°C ~10°C for 2 hours. With the addition of *N,N*-diisopropylethylamine(1.1 ml) and isopropylamine(0.55 ml), the mixture was stirred at 10°C ~15°C for 3 hours. The reaction mixture was washed with an aqueous sodium bicarbonate and water twice. The separated organic layer was
5 dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in chloroform(15 ml) and with the slow addition of ether, crystals were precipitated. For 2-hours stirring, the precipitate was filtered, washed (ether) and dried to give a desired compound of 1.74 g (yield: 78%).

10 m.p. : 143 ~145°C

¹H-NMR(CDCl₃), ppm : δ 1.28(d, 6H), 3.46(m, 2H), 3.63(m, 2H), 3.75(m, 2H), 3.97(m, 2H), 4.32(m, 1H), 6.28(m, 1H), 6.85(m, 1H), 7.72(m, 1H), 8.18(m, 2H), 8.37(m, 1H), 8.94(m, 1H)

15 Step (2) : Preparation of 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-(*N*-isopropylcarbamoyl)pyridine

A mixture of 5-(*N*-isopropylcarbamoyl)-2-[1-(3-nitro-2-pyridyl)piperazin-4-yl-carbonyl]pyridine(1.5 g), so obtained from the Step (1) and about 0.3 ml of Raney-nickel(50% slurry in water) was added to
20 methanol(30 ml) in a pressurized reactor and the reaction mixture was filled with hydrogen gas and reduced at 50~60 psi for 3 hours. After completion of the reduction, reaction mixture was filtered through celite and concentrated under reduced pressure. The concentrated residue was treated with ether for crystalization and recrystallized with ethyl acetate and isopropyl ether to give
25 a desired compound of 1.05 g (yield: 75%).

m.p. : 142 ~143°C

¹H-NMR(CDCl₃), ppm : δ 1.29(d, 2H), 3.13(m, 2H), 3.24(m, 2H), 3.67(m, 2H), 3.98(m, 2H), 4.32(m, 1H), 6.40(m, 1H), 6.86(m, 1H), 6.99(m, 1H), 7.63(m, 1H),

7.80(m, 1H), 8.15(m, 1H), 8.92(m, 1H)

Example 28 : 5-[N-(1,1-dimethylethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

5 By the same procedure as described example 24, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 2-methyl-2-propaneamine. And then, the product was recrystallized with isopropanol to give a desired compound.

Yield: 82 %

10 m.p. : 161 ~ 162 °C

¹H-NMR(CDCl₃), ppm : δ 1.27(d, 6H), 1.49(s, 9H), 3.11(m, 2H), 3.20(m, 2H), 3.54(m, 1H), 3.71(m, 2H), 3.97(m, 2H), 4.16(m, 1H), 6.05(m, 1H), 6.87(m, 1H), 6.97(m, 1H), 7.70(m, 2H), 8.14(m, 1H), 8.90(m, 1H)

15 **Example 29 : 5-[N-(1,1-dimethylethyl)carbamoyl]-2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine**

By the same procedure as described example 25, the synthesis was carried out using 2-methyl-2-propaneamine.

Yield: 70 %

20 ¹H-NMR(CDCl₃), ppm : δ 1.28(t, 3H), 1.50(s, 9H), 3.15(m, 6H), 3.71(m, 2H), 3.97(m, 2H), 4.15(m, 1H), 6.05(m, 1H), 6.88(m, 1H), 6.98(m, 1H), 7.70(m, 2H), 8.14(m, 1H), 8.91(m, 1H)

Example 30 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-methylpropyl)carbamoyl]pyridine

25 By the same procedure as described example 24, the synthesis was carried out using isobutylamine.

Yield: 82 %

m.p. : 131 ~ 134 °C

¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.25(d, 6H), 1.95(m, 1H), 3.13(m, 2H), 3.21(m, 2H), 3.33(m, 2H), 3.57(m, 1H), 3.72(m, 2H), 3.98(m, 2H), 4.16(m, 1H), 6.40(m, 1H), 6.89(m, 1H), 6.98(m, 1H), 7.70(m, 2H), 8.19(m, 1H), 8.95(m, 1H)

5

Example 31 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-methylpropyl)carbamoyl]pyridine

By the same procedure as described example 24, the synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using isobutylamine. And then, the product was recrystallized with ethanol and hexane to give a desired compound.

Yield: 77 %

¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.28(t, 3H), 1.96(m, 1H), 3.14(m, 4H), 3.23(m, 2H), 3.34(m, 2H), 3.72(m, 2H), 3.98(m, 2H), 4.16(m, 1H), 6.39(m, 1H), 6.90(m, 1H), 6.98(m, 1H), 7.71(m, 2H), 8.19(m, 1H), 8.96(m, 1H)

15

Example 32 : 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-[N-(2-methylpropyl)carbamoyl]pyridine

Step (1) : Preparation of 5-[N-(2-methylpropyl)carbamoyl]-2-[1-(3-nitro-2-pyridyl)piperazin-4-yl-carbonyl]pyridine

By the same procedure as described Step(1) of example 27, the synthesis was carried out using isobutylamine.

Yield: 80 %

¹H-NMR(CDCl₃), ppm : δ 1.02(d, 6H), 1.96(m, 1H), 3.13(m, 2H), 3.21(m, 2H), 3.33(m, 2H), 3.72(m, 2H), 3.98(m, 2H), 6.89(m, 1H), 6.98(m, 1H), 7.70(m, 2H), 8.20(m, 1H), 8.94(m, 1H)

25

Step (2) : Preparation of 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-[N-(2-methylpropyl)carbamoyl]pyridine

By the same procedure as described in the step(2) of example 27, the synthesis was carried out starting with 5-[N-(2-methylpropyl)carbamoyl]-2-[1-(3-nitro-2-pyridyl)piperazin-4-yl-carbonyl]pyridine, so prepared by Step (1) and using isobutylamine. And then, the product was recrystallized with ethanol and ether to give a desired compound.

Yield: 72 %

¹H-NMR(CDCl₃), ppm : δ 1.01(d, 6H), 1.96(m, 1H), 3.12(m, 2H), 3.22(m, 2H), 3.34(m, 2H), 3.73(m, 2H), 3.98(m, 2H), 6.39(m, 1H), 6.89(m, 1H), 6.97(m, 1H), 7.65(m, 1H), 7.78(m, 1H), 8.19(m, 1H), 8.97(m, 1H)

Example 33 : 5-(N,N-diethylcarbamoyl)-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid. And then, the product was recrystallized with ethanol and tetrahydrofuran to give a desired compound.

Yield: 78 %

m.p. : 100 ~ 102 °C

¹H-NMR(CDCl₃), ppm : δ 1.13(m, 3H), 1.24(m, 9H), 3.10(m, 2H), 3.18(m, 2H), 3.27(m, 2H), 3.56(m, 3H), 3.74(m, 2H), 3.97(m, 2H), 4.17(m, 1H), 6.86(m, 1H), 6.96(m, 1H), 7.70(m, 2H), 7.81(m, 1H), 8.63(m, 1H)

Example 34 : 5-(N,N-diisopropylcarbamoyl)-2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-

carbonyl]nicotinic acid and using diisopropylamine. And then, the product was recrystallized with acetone and hexane to give a desired compound.

Yield: 72 %

¹H-NMR(CDCl₃), ppm : δ 1.15(m, 6H), 1.24(m, 12H), 3.10(m, 2H), 3.18(m, 2H),
5 3.53(m, 3H), 3.60(m, 2H), 3.95(m, 2H), 6.87(m, 1H), 6.96(m, 1H), 7.71(m, 2H),
7.81(m, 1H), 8.64(m, 1H)

Example 35 : 5-(N-cyclopropylcarbamoyl)-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

10 By the same procedure as described in the example 25, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using cyclopropylamine. And then, the product was recrystallized with isopropanol and petroleum ether to give a desired compound.

15 Yield: 77 %

m.p. : 188 ~ 190 °C

¹H-NMR(CDCl₃), ppm : δ 0.71(m, 2H), 0.84(m, 2H), 1.25(d, 6H), 2.93(m, 1H),
3.05(m, 2H), 3.16(m, 2H), 3.55(m, 1H), 3.63(m, 2H), 3.95(m, 2H), 4.15(m, 1H),
6.83(m, 1H), 6.93(m, 1H), 7.38(m, 1H), 7.49(m, 1H), 7.67(m, 1H), 8.09(m, 1H),
20 8.87(m, 1H)

Example 36 : 5-(N-cyclopropylcarbamoyl)-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

25 By the same procedure as described in the example 25, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using cyclopropylamine. And then, the product was recrystallized with ethanol and hexane to give a desired compound.

Yield: 69 %

m.p. : 164 ~ 165 °C

¹H-NMR(CDCl₃), ppm : δ 0.65(m, 2H), 0.87(m, 2H), 0.98(d, 6H), 1.90(m, 1H),
2.89(m, 3H), 3.04(m, 2H), 3.16(m, 2H), 3.64(m, 2H), 3.94(m, 2H), 4.32(m, 1H),
5 6.78(m, 2H), 6.89(m, 1H), 7.57(m, 1H), 7.65(m, 1H), 8.08(m, 1H), 8.86(s, 1H)

Example 37 : 5-(N-cyclopentylcarbamoyl)-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 24, the synthesis
10 was carried out using cyclopentylamine.

Yield: 83 %

m.p. : 197 ~ 199 °C

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 1.56(m, 2H), 1.67-1.76(m, 4H), 2.13(m,
2H), 3.12(m, 2H), 3.20(m, 2H), 3.56(m, 1H), 3.71(m, 2H), 3.97(m, 2H), 4.17(m,
15 1H), 4.43(m, 1H), 6.39(m, 1H), 6.89(m, 1H), 6.96(m, 1H), 7.68(m, 2H), 8.16(m,
1H), 8.92(m, 1H)

Example 38 : 5-(N-cyclopentylcarbamoyl)-2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

20 By the same procedure as described in the example 24, the synthesis
was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-
carbonyl]nicotinic acid and using cyclopentylamine. And then, the product
was recrystallized with isopropanol and ether to give a desired compound.

Yield: 76 %

25 ¹H-NMR(CDCl₃), ppm : δ 1.28(t, 3H), 1.56(m, 2H), 1.68-1.77(m, 4H), 2.14(m,
2H), 3.17(m, 6H), 3.70(m, 2H), 3.98(m, 2H), 4.16(m, 1H), 4.44(m, 1H), 6.30(m,
1H), 6.87(m, 1H), 6.95(m, 1H), 7.66(m, 2H), 8.16(m, 1H), 8.90(m, 1H)

Example 39 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-methoxyethyl)carbamoyl]pyridine

By the same procedure as described in the example 25, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using 2-methoxyethylamine. And then, the product was recrystallized with methylene chloride and hexane to give a desired compound.

Yield: 73 %

m.p. : 122 ~ 124 °C

¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 3.09(m, 2H), 3.16(m, 2H), 3.38(s, 3H), 3.55(m, 3H), 3.67(m, 4H), 3.95(m, 2H), 4.13(m, 1H), 6.67(m, 1H), 6.84(m, 1H), 6.95(m, 2H), 7.69(m, 2H), 8.17(m, 1H), 8.94(m, 1H)

Example 40 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-methoxyethyl)carbamoyl]-pyridine

By the same procedure as described in the example 25, the synthesis was carried out using 2-methoxyethylamine.

Yield: 70.5 %

m.p. : 115 ~ 116 °C

¹H-NMR(CDCl₃), ppm : δ 1.31(t, 3H), 3.14(m, 4H), 3.21(m, 2H), 3.40(s, 3H), 3.57(m, 2H), 3.70(m, 4H), 3.98(m, 2H), 4.21(m, 1H), 6.71(m, 1H), 6.86(m, 1H), 6.96(m, 1H), 7.72(m, 2H), 8.20(m, 1H), 8.98(m, 1H)

Example 41 : 2-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-methoxyethyl)carbamoyl]-pyridine

By the same procedure as described in the example 25, the synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using 2-methoxyethylamine. And

then, the product was recrystallized with isopropanol to give a desired compound.

Yield: 65%

m.p. : 123 ~ 125 °C

5 ¹H-NMR(CDCl₃), ppm : δ 0.99(d, 6H), 1.89(m, 1H), 2.88(m, 2H), 3.07(m, 2H), 3.16(m, 2H), 3.37(s, 3H), 3.55(m, 2H), 3.65(m, 4H), 3.95(m, 2H), 4.33(m, 1H), 6.79(m, 2H), 6.90(m, 1H), 7.67(m, 2H), 8.16(m, 1H), 8.94(s, 1H)

Example 42 : 5-[N,N-bis(2-methoxyethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine ·HCl
10

Triethylamine(0.8 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(2 g) in methylene chloride(30 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.7 ml) at 0 °C ~ 5 °C, the mixture was stirred at 5 °C for 1 hour. With the addition of
15 N,N-diisopropylethylamine(1 ml) and bis(2-methoxyethyl)amine(0.85 ml), the mixture was stirred at 10 °C for 3 hours. The reaction mixture was washed with an aqueous sodium bicarbonate and water twice. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in chloroform and with the slow addition
20 of 4.5 ml of anhydrous 1N-hydrochloric acid(solution in isopropanol), crystals were precipitated. After mixture was stirred for 1 hour, and then filtered. The crystals, so separated, was recrystallized with methylene chloride and hexane to give a desired compound of 1.92 g (yield: 68%) as a hydrochloride salt.

¹H-NMR(CDCl₃), ppm : δ 1.33(d, 6H), 3.31-3.39(m, 6H), 3.48(m, 2H), 3.54(m, 25 6H), 3.66(m, 3H), 3.78(m, 2H), 3.95(m, 2H), 4.04(m, 2H), 7.28(m, 2H), 7.79(m, 1H), 7.88(m, 1H), 7.97(m, 1H), 8.67(m, 1H)

Example 43 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-

[N-(2-methoxy-1-methylethyl)carbamoyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out using 2-methoxyisopropylamine.

Yield: 79 %

5 m.p. : 134 ~ 135 °C

¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 1.33(d, 3H), 3.10(m, 2H), 3.18(m, 2H), 3.40(s, 3H), 3.46(m, 1H), 3.54(m, 2H), 3.72(m, 2H), 3.97(m, 2H), 4.15(m, 1H), 4.37(m, 1H), 6.54(m, 1H), 6.86(m, 1H), 6.95(m, 1H), 7.69(m, 2H), 8.17(m, 1H), 8.96(m, 1H)

10

Example 44: 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(2-methoxy-1-methylethyl)carbamoyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 2-methoxyisopropylamine. And then, the product was recrystallized with isopropanol and hexane to give a desired compound.

Yield: 82 %

¹H-NMR(CDCl₃), ppm : δ 1.30(t, 3H), 1.34(d, 3H), 3.14(m, 4H), 3.19(m, 2H), 3.41(s, 3H), 3.52(m, 2H), 3.72(m, 2H), 3.96(m, 2H), 4.15(m, 1H), 4.38(m, 1H), 6.56(m, 1H), 6.86(m, 1H), 6.97(m, 1H), 7.70(m, 2H), 8.16(m, 1H), 8.98(m, 1H)

20

Example 45 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(3-methoxypropyl)carbamoyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out using 3-methoxypropylamine. And then, the product was recrystallized with ethanol and isopropyl ether to give a desired compound.

Yield: 77 %

25

m.p. : 95 ~ 96 °C

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 1.93(m, 2H), 3.15-3.21(m, 4H), 3.40(s, 3H), 3.62(m, 5H), 3.73(m, 2H), 3.98(m, 2H), 4.17(m, 1H), 6.89(m, 1H), 6.99(m, 1H), 7.27(m, 1H), 7.73(m, 2H), 8.19(m, 1H), 8.94(m, 1H)

5

Example 46 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(3-methoxypropyl)carbamoyl]pyridine

By the same procedure as described in the example 25, the synthesis was carried out using 3-methoxypropylamine. And then, the product was recrystallized with acetonitrile and ether to give a desired compound.

10

Yield: 72 %

¹H-NMR(CDCl₃), ppm : δ 1.29(t, 3H), 1.93(m, 2H), 3.15-3.20(m, 6H), 3.41(s, 3H), 3.60(m, 4H), 3.73(m, 2H), 3.98(m, 2H), 4.17(m, 1H), 6.89(m, 1H), 6.98(m, 1H), 7.27(m, 1H), 7.73(m, 2H), 8.19(m, 1H), 8.94(m, 1H)

15

Example 47 : 2-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(3-methoxypropyl)carbamoyl]pyridine

By the same procedure as described in the example 25, the synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using 3-methoxypropylamine. And then, the product was recrystallized with methanol and isopropyl ether to give a desired compound.

20

Yield: 64 %

m.p. : 109 ~ 110 °C

25

¹H-NMR(TFA-d₄), ppm : δ 1.25(d, 6H), 2.19(m, 1H), 2.33(m, 2H), 3.28(d, 2H), 3.74(s, 3H), 3.82(m, 4H), 3.94(m, 2H), 4.02(m, 2H), 4.21(m, 2H), 4.42(m, 2H), 7.65(m, 1H), 7.73(m, 1H), 7.80(m, 1H), 8.62(m, 1H), 9.42(m, 1H), 9.78(s, 1H)

Example 48 : 5-[N-[2-(2-hydroxyethoxy)ethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 25, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid methyl ester and using 2-(2-aminoethoxy)ethanol. And then, the product was recrystallized with acetone and hexane to give a desired compound.

Yield: 79 %

m.p. : 93 ~ 95 °C

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 3.10(m, 2H), 3.21(m, 2H), 3.52(m, 1H), 3.67(m, 8H), 3.77(m, 2H), 3.96(m, 2H), 4.17(m, 1H), 6.86(m, 1H), 6.95(m, 1H), 7.49(m, 1H), 7.68(m, 2H), 8.18(m, 1H), 8.97(m, 1H)

Example 49 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-[2-(2-hydroxyethoxy)ethyl]carbamoyl]pyridine

By the same procedure as described in the example 25, the synthesis was carried out using 2-(2-aminoethoxy)ethanol.

Yield: 75 %

¹H-NMR(CDCl₃), ppm : δ 1.30(t, 3H), 3.14(m, 4H), 3.21(m, 2H), 3.67(m, 8H), 3.76(m, 2H), 3.96(m, 2H), 4.16(m, 1H), 6.87(m, 1H), 6.95(m, 1H), 7.49(m, 1H), 7.68(m, 2H), 8.18(m, 1H), 8.97(m, 1H)

Example 50 : 5-[N-(2,2-dimethoxyethyl)-N-methylcarbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine ·HCl

By the same procedure as described in the example 42, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using methylaminoacetaldehyde dimethyl acetal to give a desired compound as a hydrochloride salt.

Yield: 70 %

¹H-NMR(CDCl₃), ppm : δ 1.33(d, 6H), 3.15(s, 3H), 3.50(m, 8H), 3.66(m, 1H), 3.94(m, 4H), 4.10(m, 4H), 4.70(m, 2H), 7.34(m, 2H), 7.85(m, 2H), 8.76(m, 1H), 9.72(m, 1H)

5

Example 51 : 5-[N-(2,2-dimethoxyethyl)carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 2,2-dimethoxyethylamine. And then, the product was crystallized with ethanol and hexane to give a desired compound.

Yield: 78 %

m.p. : 167 ~ 169 °C

¹H-NMR(CDCl₃), ppm : δ 1.16(d, 6H), 3.01(m, 2H), 3.10(m, 2H), 3.38(s, 6H), 3.48(m, 1H), 3.57(m, 2H), 3.64(m, 2H), 3.90(m, 2H), 4.08(m, 1H), 4.44(m, 1H), 6.44(m, 1H), 6.78(m, 1H), 6.86(m, 1H), 7.61(m, 2H), 8.12(m, 1H), 8.90(s, 1H)

15

Example 52 : 5-[N-[(1,3-Dioxolan-2-yl)methyl]-N-methylcarbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried using 2-methylaminomethyl-1,3-dioxolan.

Yield: 67 %

m.p. : 108 ~ 110 °C

¹H-NMR(TFA-d₄), ppm : δ 1.53(d, 6H), 3.62(s, 3H), 3.70(m, 2H), 3.79(m, 2H), 3.94(m, 2H), 4.11(m, 2H), 4.41(m, 3H), 4.79(m, 1H), 4.92(t, 4H), 7.65(m, 1H), 7.78(m, 2H), 8.53(m, 1H), 9.04(m, 1H), 9.54(s, 1H)

25

Example 53 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-

[N-(tetrahydrofuran-2-yl-methyl)carbamoyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using tetrahydrofurfurilamine. And then, the product was crystallized with ethanol and hexane to give a desired compound.

Yield: 83 %

m.p. : 108 ~ 110 °C

¹H-NMR(CDCl₃), ppm : δ 1.26(d, 6H), 1.63(m, 1H), 1.98(m, 2H), 2.07(m, 1H), 3.18 ~ 3.23(m, 4H), 3.38(m, 1H), 3.57(m, 1H), 3.78(m, 4H), 3.83(m, 1H), 3.91(m, 2H), 4.09(m, 1H), 4.11(m, 1H), 6.66(m, 1H), 6.93(m, 1H), 6.99(m, 1H), 7.73(m, 2H), 8.19(m, 1H), 8.98(m, 1H)

Example 54 : 2-[1-[3-(Ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(tetrahydrofuran-2-yl-methyl)carbamoyl]pyridine

By the same procedure as described in the example 24, the synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using tetrahydrofurfurilamine. And then, the product was crystallized with ethyl acetate and hexane to give a desired compound.

Yield: 77 %

¹H-NMR(CDCl₃), ppm : δ 1.29(t, 3H), 1.63(m, 1H), 1.99(m, 2H), 2.06(m, 1H), 3.18 ~ 3.22(m, 6H), 3.38(m, 1H), 3.78(m, 4H), 3.82(m, 1H), 3.92(m, 2H), 4.09(m, 1H), 4.11(m, 1H), 6.67(m, 1H), 6.92(m, 1H), 6.98(m, 1H), 7.73(m, 1H), 8.19(m, 1H), 8.99(m, 1H)

Example 55 : 2-[1-[3-(Isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(tetrahydro-2-fuanon-3-yl)carbamoyl]pyridine

Triethylamine(0.8 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(2 g) in methylene chloride(40

ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.7 ml) at 0°C ~ 5°C, the mixture was stirred at 5°C for 1 hour. With the addition of triethylamine(2.2 ml) and α -amino- γ -butyrolactone hydrobromide (1.4 g), the mixture was stirred at 10°C for 3 hours. The reaction mixture was washed
5 with an aqueous sodium bicarbonate and water twice. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in a small amount of chloroform and with the addition of ether, crystals were precipitated. The mixture was stirred for 1 hour and filtered. The solid was recrystallized with acetonitrile and hexane to
10 give a desired compound of 1.84 g (yield: 75%) .

m.p. : 199 ~ 201 °C

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 2.42(m, 1H), 2.83(m, 1H), 3.10(m, 2H), 3.18(m, 2H), 3.56(m, 1H), 3.67(m, 2H), 3.96(m, 2H), 4.13(m, 1H), 4.36(m, 1H), 4.55(m, 1H), 4.81(m, 1H), 6.86(m, 1H), 6.95(m, 1H), 7.68(m, 2H), 7.81(m, 1H),
15 8.19(m, 1H), 8.97(m, 1H)

Example 56 : 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-[N-(tetrahydro-2-furanon-3-yl)carbamoyl]pyridine

6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid(1 g)
20 was added to a co-solvent of tetrahydrofuran(25 ml) and methylene chloride(15 ml) and with the successive addition of 1,3-dicyclohexylcarbodiimide(1.3 g) and 1-hydroxybenzotriazole(0.46 g) at 15°C ~ 20°C, the mixture was stirred for 2 hours. A mixture of α -amino- γ -butyrolactone hydrobromide (1.1 g) and triethylamine(0.9 ml) was added
25 again to the mixture at 20°C and stirred at 20°C ~ 25°C for 3 hours. With the addition of methylene chloride(50 ml), the mixture was washed with water 3 times, dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization and

recrystallized with chloroform and tetrahydrofuran to give a desired compound of 1.07 g (yield: 71%).

¹H-NMR(CDCl₃), ppm : δ 2.44(m, 1H), 2.67(m, 1H), 3.18(m, 2H), 3.26(m, 2H), 3.70(m, 2H), 3.98(m, 2H), 4.35(m, 1H), 4.53(m, 1H), 4.87(m, 1H), 6.92(m, 1H),
5 7.12(m, 1H), 7.72(m, 2H), 8.38(m, 1H), 9.14(m, 2H)

Example 57 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-(tetrahydro-2-thiophenon-3-yl)carbamoyl]pyridine

By the same procedure as described in the example 55, synthesis was
10 carried out using homocysteine thiolactone hydrochloride.

Yield: 68 %

m.p. : 195 ~ 196 °C

¹H-NMR(CDCl₃), ppm : δ 1.26(d, 6H), 2.21(m, 1H), 2.96(m, 1H), 3.08(m, 2H), 3.17(m, 2H), 3.32(m, 1H), 3.41(m, 1H), 3.54(m, 1H), 3.64(m, 2H), 3.96(m, 2H),
15 4.12(m, 1H), 4.81(m, 1H), 6.84(m, 1H), 6.95(m, 1H), 7.47(m, 1H), 7.68(m, 2H), 8.17(m, 1H), 8.96(m, 1H)

Example 58 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-[3-(2-pyrrolidinon-1-yl)propyl]carbamoyl]pyridine HCl

20 By the same procedure as described in the example 42, synthesis was carried out starting with 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 1-(3-aminopropyl)-2-pyrrolidinone.

Yield: 63 %

¹H-NMR(TFA-d₁), ppm : δ 1.64(d, 6H), 2.43(m, 2H), 2.63(m, 2H), 3.28(m, 2H),
25 3.95(m, 8H), 4.10(m, 3H), 4.30(m, 2H), 4.51(m, 2H), 7.79(m, 1H), 7.93(m, 2H), 8.76(m, 1H), 9.56(m, 1H), 9.92(s, 1H)

Example 59 : 2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-

[N-[2-(morpholin-4-yl)ethyl]carbamoyl]pyridine

By the same procedure as described in the example 24, synthesis was carried out using 4-(2-aminoethyl)morpholine.

Yield: 75 %

5 ¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 2.62(m, 4H), 2.72(m, 2H), 3.08(m, 2H), 3.18(m, 2H), 3.53(m, 1H), 3.63(m, 2H), 3.72(m, 2H), 3.80(m, 4H), 3.98(m, 2H), 4.15(m, 1H), 6.84(m, 1H), 6.94(m, 1H), 7.67(m, 1H), 7.76(m, 1H), 8.26(m, 1H), 8.99(m, 1H)

10 **Example 60 : 2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-5-[N-[2-(morpholin-4-yl)ethyl]carbamoyl]pyridine ·HCl**

By the same procedure as described in the example 42, synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 4-(2-aminoethyl)morpholine.

15 Yield: 70 %

m.p. : 223 ~ 225 °C

¹H-NMR(TFA-d₁), ppm : δ 1.48(t, 3H), 3.45(m, 4H), 3.82(m, 6H), 4.02(m, 2H), 4.13(m, 2H), 4.30(m, 6H), 4.47(m, 2H), 7.56(m, 1H), 7.67(m, 1H), 7.77(m, 1H), 8.59(m, 1H), 9.43(m, 1H), 9.80(m, 1H)

20

Example 61 : 2-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-5-[N-[2-(morpholin-4-yl)ethyl]carbamoyl]pyridine

By the same procedure as described in the example 56, synthesis was carried out using 4-(2-aminoethyl)morpholine. And then, the product was
25 recrystallized with ethyl acetate and ether to give a desired compound.

Yield: 73 %

¹H-NMR(CDCl₃), ppm : δ 2.63(m, 4H), 2.74(m, 2H), 3.08(m, 2H), 3.18(m, 2H), 3.64(m, 2H), 3.73(m, 2H), 3.83-3.96(m, 6H), 6.84(m, 1H), 6.95(m, 1H), 7.67(m,

1H), 7.76(m, 1H), 8.26(m, 1H), 8.98(m, 1H)

Example 62 : 5-[N-[2-(dimethylamino)ethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine ·HCl

5 By the same procedure as described in the example 42, synthesis was carried out using *N,N*-dimethylethylenediamine. And then, the product was recrystallized with acetone and petroleum ether to give a desired compound as hydrochloride salt.

Yield: 72 %

10 ¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 2.84(s, 6H), 3.10(m, 4H), 3.26(m, 2H), 3.54(m, 3H), 3.95(m, 4H), 4.16(m, 1H), 6.83(m, 1H), 6.92(m, 1H), 7.67(m, 2H), 8.49(m, 1H), 8.96(m, 1H), 9.26(m, 1H)

Example 63 : 5-[N-[2-(dimethylamino)ethyl]carbamoyl]-2-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine ·HCl

15 By the same procedure as described in the example 42, synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using *N,N*-dimethylethylenediamine. And then, the product was recrystallized with acetone and ether to give a desired compound as a hydrochloride salt.

Yield: 67 %

¹H-NMR(CDCl₃), ppm : δ 1.28(t, 3H), 2.79(s, 6H), 3.10(m, 6H), 3.26(m, 2H), 3.54(m, 2H), 3.93(m, 4H), 4.16(m, 1H), 6.82(m, 1H), 6.93(m, 1H), 7.67(m, 2H), 8.46(m, 1H), 8.97(m, 1H), 9.26(m, 1H)

25

Example 64 : 5-[N-[2-(diethylamino)ethyl]carbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine ·HCl

By the same procedure as described in the example 42, synthesis was

carried out using 2-(diethylamino)ethylamine.

Yield: 76 %

¹H-NMR(CDCl₃), ppm : δ 1.02(m, 6H), 1.25(d, 6H), 3.10(m, 8H), 3.27(m, 2H),
3.53(m, 3H), 3.95(m, 4H), 4.16(m, 1H), 6.83(m, 1H), 6.94(m, 1H), 7.67(m, 2H),
5 8.47(m, 1H), 8.97(m, 1H), 9.27(m, 1H)

Example 65 : 5-[N-[3-(dimethylamino)propyl]-N-methylcarbamoyl]-2-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]pyridine

By the same procedure as described in the example 24, synthesis was
10 carried out using *N,N,N'*-trimethyl-1,3-propanediamine. And then, the
product was recrystallized with acetonitrile and isopropyl ether to give a
desired compound.

Yield: 70 %

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 2.80(s, 6H), 3.01(s, 3H), 3.10(m, 4H),
15 3.26(m, 2H), 3.54(m, 3H), 3.95(m, 4H), 4.16(m, 1H), 6.83(m, 1H), 6.92(m, 1H),
7.67(m, 2H), 8.96(m, 1H), 9.26(m, 1H)

Example 66 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(5-methyl-1H-pyrazol-3-yl)nicotinamide

20 Triethylamine(0.8 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(2 g) in methylene chloride(30 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.7 ml) at 0℃ ~ 5℃, the mixture was stirred at 5℃ for 1 hour. With the addition of triethylamine(0.9 ml) and 3-amino-5-methylpyrazole(0.56 g), the mixture was
25 stirred at 5℃ ~ 10℃ for 3 hours. The solution was slowly heated and stirred at 15℃ ~ 20℃ for 30 minutes. The solution was washed with an aqueous sodium bicarbonate and water twice. The separated organic layer was concentrated under reduced pressure. The concentrated residue was chromatographed on

column (chloroform/isopropanol = 10/1, v/v). The purified solution was recovered and concentrated under reduced pressure. The residue was treated with ether for crystallization and with the addition of isopropyl ether(20 ml), and stirred for 2 hours, filtered and washed to give a desired compound of
5 1.77 g (yield: 73%).

m.p. : 116~117°C

¹H-NMR(CDCl₃), ppm : δ 1.26(d, 6H), 2.17(s, 3H), 3.12(m, 2H), 3.21(m, 2H), 3.55(m, 1H), 3.78(m, 2H), 3.99(m, 2H), 4.16(m, 1H), 5.34(s, 1H), 5.63(bs, 1H), 6.86(m, 1H), 6.96(m, 1H), 7.70(m, 1H), 7.76(m, 1H), 8.53(m, 1H), 9.25(m, 1H)

10

Example 67 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(5-methylisoxazol-3-yl)nicotinamide

By the same procedure as described in the example 66, synthesis was carried out using 3-amino-5-methylisoxazole.

15 Yield: 75 %

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 2.44(s, 3H), 3.16(m, 4H), 3.55(m, 1H), 3.75(m, 2H), 3.98(m, 2H), 4.15(m, 1H), 6.87(m, 2H), 6.96(m, 1H), 7.68(m, 1H), 7.77(m, 1H), 8.39(m, 1H), 9.15(m, 1H), 10.40(s, 1H)

20

Example 68 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(4-methyl-1,3-thiazol-2-yl)nicotinamide

By the same procedure as described in the example 66, synthesis was carried out using 2-amino-4-methylthiazole.

Yield: 69 %

25 m.p. : 128~130°C

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 2.21(s, 3H), 3.14(m, 4H), 3.56(m, 1H), 3.73(m, 2H), 4.01(m, 2H), 4.16(m, 1H), 6.61(s, 1H), 6.88(m, 1H), 6.96(m, 1H), 7.70(m, 1H), 7.76(m, 1H), 8.35(m, 1H), 9.13(m, 1H)

Example 69 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(1,3,4-thiadiazol-2-yl)nicotinamide

By the same procedure as described in the example 66, synthesis was
5 carried out using 2-amino-1,3,4-thiadiazole. And then, the product was
recrystallized with ethyl acetate and hexane to give a desired compound.

Yield: 64 %

m.p. : 260 ~ 262 °C

¹H-NMR(TFA-d₁), ppm : δ 1.45(d, 6H), 3.67(m, 4H), 3.86(m, 1H), 4.09(m, 2H),
10 4.34(m, 2H), 7.56(m, 1H), 7.72(m, 2H), 8.61(m, 1H), 9.53(m, 1H), 9.92(m, 2H)

Example 70 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(2-pyridyl)nicotinamide

Thionyl chloride(0.3 ml) was added to 6-[1-[3-(isopropylamino)-2-
15 pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(1 g) in methylene chloride(25
ml), and the mixture was heated and stirred at 35 °C for 2 hours. With the
addition of 2-aminopyridine(1 g) and acetonitrile(5 ml), the mixture was
stirred at 30 °C ~ 35 °C for 5 hours. The mixture was cooled to room
temperature and washed with water and an aqueous sodium bicarbonate. The
20 separated organic layer was concentrated under reduced pressure. The
concentrated residue was chromatographed on column
(hexane/chloroform/methanol = 5/4/2, v/v/v). The purified solution was
recovered and concentrated under reduced pressure. The residue was treated
with ether (25 ml) for crystallization. After a 1-hour stirring, the residue was
25 filtered and washed to give a desired compound of 0.86 g (yield: 71%).

m.p. : 164 ~ 165 °C

¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 3.14(m, 4H), 3.52(m, 1H), 3.71(m, 2H),
3.96(m, 2H), 4.15(m, 1H), 6.83(m, 1H), 6.92(m, 1H), 7.08(m, 1H), 7.65(m, 1H),

7.76(m, 2H), 8.22(m, 1H), 8.34(m, 2H), 9.10(m, 2H)

Example 71 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(6-methoxy-3-pyridyl)nicotinamide

5 By the same procedure as described in the example 70, synthesis was carried out using 5-amino-2-methoxypyridine.

Yield: 63 %

m.p. : 173 ~ 176 °C

¹H-NMR(CDCl₃), ppm : δ 1.25(d, 6H), 3.11(m, 2H), 3.21(m, 2H), 3.56(m, 1H),
10 3.76(m, 2H), 3.92(m, 3H), 3.99(m, 2H), 4.16(m, 1H), 6.78(m, 1H), 6.89(m, 1H),
6.97(m, 1H), 7.51(m, 1H), 7.69(m, 1H), 8.16(m, 2H), 8.49(m, 1H), 8.99(s, 1H),
9.36(s, 1H)

Example 72 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(pyrazine-2-yl)nicotinamide

15 By the same procedure as described in the example 70, synthesis was carried out using aminopyrazine.

Yield: 68 %

m.p. : 209 ~ 210 °C

20 ¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 3.18(m, 4H), 3.56(m, 1H), 3.72(m, 1H),
3.98(m, 2H), 4.13(m, 1H), 6.92(m, 2H), 7.67(m, 1H), 7.75(m, 1H), 8.32(m, 2H),
8.42(m, 1H), 8.95(s, 1H), 9.12(m, 1H), 9.67(s, 1H)

Example 73 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(2-pyridylmethyl)nicotinamide · HCl

25 Triethylamine(0.8 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(2 g) in methylene chloride(30 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.7

ml) at 0°C ~ 5°C, the mixture was stirred at 5°C for 1 hour. With the addition of *N,N*-diisopropylethylamine(1 ml) and 2-(aminomethyl)pyridine(0.65 g), the mixture was stirred at 10°C for 2 hours. The solution was washed with an aqueous sodium bicarbonate and water. The separated organic layer was dried
5 over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was chromatographed on column (chloroform/isopropanol = 7/1, v/v). The purified solution was recovered and concentrated under reduced pressure. The residue was dissolved in methylene chloride(20 ml) and with the addition of 1.9 ml of anhydrous
10 hydrochloric acid(2N-ethanol solution), the residue was concentrated under reduced pressure. The residue was dissolved again in methylene chloride(10 ml) and concentrated under reduced pressure. Then, the residue was treated with ether(20 ml) for crystallization and concentrated under reduced pressure to give a desired compound of 1.75 g (yield: 65%) as a hydrochloride salt.

15 ¹H-NMR(CDCl₃), ppm : δ 1.27(d, 6H), 3.25(m, 4H), 3.58(m, 1H), 3.75(m, 2H), 3.98(m, 2H), 4.15(m, 1H), 4.86(m, 2H), 7.01(m, 2H), 7.43(m, 1H), 7.56(m, 1H), 7.76(m, 2H), 7.92(m, 1H), 8.36(m, 2H), 8.61(m, 1H), 9.12(m, 1H)

Example 74 : 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-*N*-(2-pyridylmethyl)nicotinamide
20

By the same procedure as described in the example 73, synthesis was carried out starting with 6-[1-[3-(ethylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 2-(aminomethyl)pyridine. And then, the product was chromatographed on column (hexane/methylene chloride/ethyl
25 acetate = 2/1/1, v/v/v) and crystallized with ether to give a desired compound.

Yield: 70 %

m.p. : 129 ~ 131 °C

¹H-NMR(CDCl₃), ppm : δ 1.28(t, 3H), 3.21(m, 6H), 3.73(m, 2H), 3.98(m, 2H), 4.21(m, 1H), 4.80(m, 2H), 6.85(m, 1H), 6.96(m, 1H), 7.25(m, 1H), 7.37(m, 1H), 7.75(m, 3H), 7.98(s, 1H), 8.29(m, 1H), 8.57(m, 1H), 9.10(m, 1H)

5 **Example 75 : 6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]-N-(2-pyridylmethyl)nicotinamide ·HCl**

By the same procedure as described in the example 73, synthesis was carried out using 6-[1-(3-amino-2-pyridyl)piperazin-4-yl-carbonyl]nicotinic acid.

10 Yield: 60 %

¹H-NMR(TFA-d₁), ppm : δ 3.92(m, 4H), 4.22(m, 2H), 4.43(m, 2H), 5.37(d, 2H), 7.56(m, 1H), 7.98(m, 2H), 8.19(m, 1H), 8.38(m, 1H), 8.69(m, 1H), 8.80(m, 1H), 8.98(m, 1H), 9.51(m, 1H), 9.88(s, 1H)

15 **Example 76 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(3-pyridylmethyl)nicotinamide**

6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(2 g) was added to a co-solvent of tetrahydrofuran(30 ml) and methylene chloride(30 ml) and with the successive addition of 1,3-dicyclohexylcarbodiimide(2.4 g) and 1-hydroxybenzotriazole(0.85 g) at 15°C ~ 20°C, the mixture was reacted at the same temperature for 2 hours. With the addition of 3-(aminomethyl)pyridine(0.65 g) at 20°C, the reaction mixture was stirred at 20°C ~ 25°C for 2 hours. With the addition of methylene chloride(60 ml), The mixture was washed with water 3 times, dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was chromatographed on column (hexane/chloroform/ethanol = 5/2/1, v/v/v). The purified solution was concentrated under reduced pressure, and then, the residue was treated with ether for crystallization to give a desired

25

compound of 1.87 g (yield: 75%).

m.p. : 164 ~ 166 °C

¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 3.08(m, 2H), 3.16(m, 2H), 3.55(m, 1H),
3.66(m, 2H), 3.92(m, 2H), 4.14(m, 1H), 4.68(m, 2H), 6.84(m, 1H), 6.94(m, 1H),
5 7.35(m, 1H), 7.62(m, 1H), 7.68(m, 2H), 7.84(m, 1H), 8.19(m, 1H), 8.53(m, 1H),
8.65(m, 1H), 9.01(s, 1H)

Example 77 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-(4-pyridylmethyl)nicotinamide

10 By the same procedure as described in the example 76, synthesis was carried out using 4-(aminomethyl)pyridine.

Yield: 72 %

m.p. : 171 ~ 173 °C

¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 3.05(m, 2H), 3.12(m, 2H), 3.55(m, 1H),
15 3.65(m, 2H), 3.89(m, 2H), 4.15(m, 1H), 4.67(d, 2H), 6.83(m, 1H), 6.94(m, 1H),
7.27(m, 2H), 7.57(m, 1H), 7.66(m, 2H), 8.15(m, 1H), 8.58(m, 2H), 8.97(m, 1H)

Example 78 : N-[[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methyl]-6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide

20 By the same procedure as described in the example 76, synthesis was carried out using 4-(aminomethyl)-5-hydroxy-6-methyl-3-pyridinemethanol dihydrochloride and triethylamine(2 equivalents).

Yield: 64 %

m.p. : 118 ~ 122 °C

25 ¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 2.46(s, 3H), 3.04(m, 2H), 3.14(m, 2H),
3.61(m, 3H), 3.92(m, 2H), 4.14(m, 1H), 4.63(d, 2H), 4.73(s, 2H), 6.83(m, 1H),
6.93(m, 1H), 7.50(m, 1H), 7.65(m, 1H), 7.77(s, 1H), 8.13(m, 1H), 8.28(m, 1H),
8.67(s, 1H)

Example 79 : *N*-(2-Furylmethyl)-6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide ·HCl

By the same procedure as described in the example 73, synthesis was
5 carried out using Furfurylamine.

Yield: 61 %

m.p. : 173 ~ 176 °C

¹H-NMR(CDCl₃), ppm : δ 1.33(d, 6H), 3.50(m, 4H), 3.64(m, 1H), 3.86(m, 2H),
4.02(m, 2H), 4.68(d, 2H), 6.34(s, 2H), 7.25(m, 2H), 7.38(s, 1H), 7.70(m, 2H),
10 7.81(m, 1H), 8.28(m, 1H), 8.99(s, 1H)

Example 80 : *N*-[2-(1H-imidazol-4-yl)ethyl]-6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide

By the same procedure as described in the example 76, synthesis was
15 carried out using histamine.

Yield: 72 %

m.p. : 98 ~ 102 °C

¹H-NMR(CDCl₃), ppm : δ 1.24(d, 6H), 2.96(m, 2H), 3.07(m, 2H), 3.15(m, 2H),
3.53(m, 1H), 3.67(m, 2H), 3.74(m, 2H), 3.95(m, 2H), 4.15(m, 1H), 6.83(m, 1H),
20 6.94(m, 2H), 7.67(m, 2H), 7.81(m, 1H), 8.28(m, 1H), 8.46(m, 1H), 9.08(s, 1H)

Example 81 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-*N*-[2-(2-thienyl)ethyl]nicotinamide

Triethylamine(0.8 ml) was added to 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid(2g) in methylene chloride(30
25 ml) for dissolution and cooled. With the slow addition of pivaloyl chloride(0.7 ml) at 0 °C ~ 5 °C, the mixture was stirred at 5 °C for 1 hour. With the successive addition of triethylamine(0.9 ml) and 2-thiophenethylamine(0.75 g), the

mixture was stirred at 5°C ~ 10°C for 2 hours. The solution was washed with an aqueous sodium bicarbonate and water. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The concentrated residue was treated with ether for crystallization. The solid, so
5 obtained, was recrystallized with ethanol and hexane to give a desired compound of 1.92 g (yield: 74%).

m.p. : 131 ~ 134 °C

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 3.03(m, 2H), 3.16(m, 4H), 3.53(m, 1H),
3.64(m, 2H), 3.73(m, 2H), 3.91(m, 2H), 4.14(m, 1H), 6.87(m, 5H), 7.16(m, 1H),
10 7.55(m, 1H), 7.63(m, 1H), 8.08(m, 1H), 8.85(m, 1H)

Example 82 : 6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]-N-[2-(2-pyridyl)ethyl]nicotinamide

By the same procedure as described in the example 81, synthesis was
15 carried out using 2-(2-aminoethyl)pyridine.

Yield: 68 %

m.p. : 79 ~ 82 °C

¹H-NMR(CDCl₃), ppm : δ 1.22(d, 6H), 3.07(m, 6H), 3.52(m, 1H), 3.66(m, 2H),
3.84(m, 2H), 3.94(m, 2H), 4.14(m, 1H), 6.81(m, 1H), 6.88(m, 1H), 7.20(m, 2H),
20 7.65(m, 3H), 8.15(m, 1H), 8.21(m, 1H), 8.54(m, 1H), 8.96(m, 1H)

Example 83 : N-[3-(1H-imidazol-1-yl)propyl]-6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide

By the same procedure as described in the example 81, synthesis was
25 carried out using 1-(3-aminopropyl)imidazole. And then, the product was crystallized with methylene chloride and ether to give a desired compound.

Yield: 71 %

m.p. : 105 ~ 108 °C

¹H-NMR(CDCl₃), ppm : δ 1.23(d, 6H), 2.16(m, 2H), 3.05(m, 2H), 3.16(m, 2H), 3.48(m, 2H), 3.54(m, 1H), 3.64(m, 2H), 3.94(m, 2H), 4.13(m, 2H), 6.82(m, 1H), 6.94(m, 1H), 7.06(m, 2H), 7.57(m, 1H), 7.65(m, 1H), 7.76(m, 1H), 7.89(m, 1H), 8.18(m, 1H), 8.99(s, 1H)

5

Example 84 : N-[3-(1H-imidazol-1-yl)propyl]-6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide

By the same procedure as described in the example 81, synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 1-(3-aminopropyl)imidazole. And then, the product was recrystallized with isopropanol to give a desired compound.

Yield: 66 %

¹H-NMR(TFA-d₁), ppm : δ 1.23(d, 6H), 2.17(m, 1H), 2.58(m, 2H), 3.26(d, 2H), 3.84(m, 6H), 4.18(m, 2H), 4.40(m, 2H), 4.60(m, 2H), 7.65(m, 4H), 7.78(m, 1H), 8.62(m, 1H), 8.92(m, 1H), 9.39(m, 1H), 9.78(s, 1H)

15

Example 85 : N-(3-hydroxy-2-pyridyl)-6-[1-[3-(isopropylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide

By the same procedure as described in the example 70, synthesis was carried out using 2-amino-3-hydroxypyridine.

20

Yield: 62 %

m.p. : 116 ~ 119°C

¹H-NMR(DMSO-d₆), ppm : δ 1.17(d, 6H), 2.94(m, 2H), 3.03(m, 2H), 3.55(m, 3H), 3.86(m, 2H), 4.45(m, 1H), 6.91(m, 2H), 7.21(m, 1H), 7.34(m, 1H), 7.55(m, 1H), 7.73(m, 1H), 7.95(m, 1H), 8.43(m, 1H), 9.14(s, 1H), 9.87(s, 1H), 10.73(s, 1H)

25

Example 86 : N-(3-hydroxy-2-pyridyl)-6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinamide

By the same procedure as described in the example 70, synthesis was carried out starting with 6-[1-[3-(isobutylamino)-2-pyridyl]piperazin-4-yl-carbonyl]nicotinic acid and using 1-(3-aminopropyl)imidazole.

Yield: 60 %

5 m.p. : 165 ~ 167°C

¹H-NMR(TFA-d₄), ppm : δ 1.85(d, 6H), 2.14(m, 1H), 3.23(d, 2H), 3.74(m, 4H), 4.12(m, 2H), 4.39(m, 2H), 7.72(m, 4H), 8.25(m, 2H), 8.61(m, 1H), 9.49(m, 1H), 9.87(s, 1H)

10 **Example 87 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-isopropylnicotinamide ·HCl**

6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(3 g) was dissolved in methanol(40 ml) and with the addition of isopropylamine(6 ml), the mixture was heated to reflux for 12 hours. The
15 mixture was concentrated under reduced pressure to remove the solvent and the excess of isopropylamine. The concentrated residue was chromatographed on column (hexane/chloroform/methanol = 7/5/1). The purified solution was recovered and concentrated under reduced pressure, and was dissolved in chloroform. To this solution, 2N-hydrochloride solution in isopropanol (4.3
20 ml) was added, and ether was added gradually for precipitation. After a 1-hour stirring, the precipitate was filtered and washed (ether) to give a desired compound of 2.74 g(yield: 75 %) as hydrochloride salt.

¹H-NMR(TFA-d₄), ppm : δ 1.52(d, 6H), 3.81(m, 4H), 4.10(m, 1H), 4.22(m, 2H), 4.46(m, 4H), 4.58(m, 1H), 5.22(m, 1H), 8.65(d, 1H), 9.41(d, 1H), 9.80(s, 1H)

25

Example 88 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-isobutylnicotinamide ·HCl

By the same procedure as described in the example 87, the synthesis

was carried out using isobutylamine.

Yield: 70 %

¹H-NMR(TFA-*d*₁), ppm : δ 1.20(d, 6H), 2.18(m, 1H), 3.60(m, 2H), 3.80(m, 4H),
4.01(m, 1H), 4.21(m, 2H), 4.45(m, 4H), 5.15(m, 1H), 8.64(d, 1H), 9.41(d, 1H),
5 9.79(s, 1H)

Example 89 : N-ethyl-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide HCl

6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl
10 ester(3 g) was dissolved in ethanol(25 ml) and with the addition of 70%
ethylamine solution(8 ml), the mixture was heated to reflux for 6 hours. The
mixture was concentrated under reduced pressure to remove the solvent and
the excess of ethylamine, dissolved in chloroform and dried over magnesium
sulfate. The residue was chromatographed on column
15 (hexane/chloroform/methanol = 10/5/2). The purified solution was
recovered and concentrated under reduced pressure, and was dissolved in
isopropanol. To this solution, 2N-hydrochloride solution in isopropanol(4.3
ml) was added, and ether was added gradually for precipitation. The
precipitate was filtered and isolated to give a desired compound of 2.38
20 g(yield: 68 %) as hydrochloride salt.

¹H-NMR(CDCl₃), ppm : δ 1.28(t, 3H), 2.56(m, 2H), 2.64(m, 4H), 3.50(m, 2H),
3.57(m, 2H), 3.67(m, 2H), 3.85(m, 2H), 6.57(m, 1H), 7.63(d, 2H), 8.14(m, 1H),
8.92(s, 1H)

25 Example 90 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-propylnicotinamide ·HCl

By the same procedure as described in the example 87, the synthesis
was carried out using propylamine.

Yield: 65 %

¹H-NMR(CDCl₃), ppm : δ 0.98(t, 3H), 1.92(m, 2H), 2.51(m, 2H), 2.65(m, 4H), 3.51(m, 5H), 3.68(m, 2H), 3.83(m, 2H), 6.58(m, 1H), 7.64(d, 2H), 8.14(m, 1H), 8.93(m, 1H)

5

Example 91 : N-cyclopropyl-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide ·HCl

By the same procedure as described in the example 87, the synthesis was carried out using cyclopropylamine.

10 Yield: 69 %

¹H-NMR(TFA-d₁), ppm : δ 0.71(m, 2H), 0.87(m, 2H), 2.91(m, 1H), 3.72(m, 4H), 4.12(m, 3H), 4.46(m, 4H), 4.59(m, 1H), 8.65(d, 1H), 9.42(d, 1H), 9.81(s, 1H)

Example 92 : N-cyclopropylmethyl-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide ·HCl

15

By the same procedure as described in the example 87, the synthesis was carried out using (aminomethyl)cyclopropane.

Yield: 76 %

¹H-NMR(TFA-d₁), ppm : δ 0.31(m, 1H), 0.72(m, 2H), 0.87(m, 2H), 3.61(m, 2H), 3.81(m, 4H), 4.01(m, 1H), 4.21(m, 2H), 4.45(m, 4H), 5.15(m, 1H), 8.64(d, 1H), 9.41(d, 1H), 9.79(s, 1H)

20

Example 93 : N-(2-hydroxyethyl)-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide

25

6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(2 g) was dissolved in methanol(20 ml) and with the addition of ethanolamine(2 ml), the mixture was heated to reflux for 8 hours and concentrated under reduced pressure. The concentrated residue was dissolved

in isopropanol(14 ml), and with the addition of isopropyl ether to precipitate. After 2-hours stirring, the filtered solid was recrystallized with ethyl acetate and hexane to give a desired compound of 1.74 g(yield: 79 %).

m.p. : 126~128°C

5 ¹H-NMR(TFA-*d*₁), ppm : δ 3.71(m, 4H), 4.01(m, 3H), 4.23(m, 5H), 4.41(m, 3H), 5.13(m, 1H), 8.57(d, 1H), 9.38(m, 1H), 9.78(s, 1H)

Example 94 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-[(1R)-1-(hydroxymethyl)propyl]nicotinamide ·HCl

10 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(3 g) was dissolved in ethanol(30 ml) and with the addition of (R)-(-)-2-amino-1-butanol(4 ml), the mixture was heated to reflux for 10 hours and concentrated under reduced pressure. The residue was chromatographed on column (hexane/ethyl acetate/ethanol = 5/3/1). The purified solution was
15 recovered and concentrated under reduced pressure, and was dissolved in methylene chloride. To this solution, 2N-hydrochloride solution in isopropanol(4.2ml) was added, and ether was added gradually for precipitation. After 2-hours stirring, the mixture was filtered to give a desired compound of 2.85 g(yield: 72 %) as a hydrochloride salt.

20 ¹H-NMR(TFA-*d*₁), ppm : δ 1.21(t, 3H), 1.91(m, 2H), 3.77(m, 4H), 4.01(m, 1H), 4.25(m, 4H), 4.43(m, 3H), 4.53(m, 1H), 5.18(m, 1H), 8.62(d, 1H), 9.42(d, 1H), 9.81(s, 1H)

Example 95 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-[(1S)-1-(hydroxymethyl)propyl]nicotinamide ·HCl
25

By the same procedure as described in the example 94, the synthesis was carried out using (S)-(+)-2-amino-1-butanol.

Yield: 67 %

¹H-NMR(TFA-*d*₁), ppm : δ 1.22(t, 3H), 1.92(m, 2H), 3.77(m, 4H), 3.99(m, 1H), 4.23(m, 4H), 4.43(m, 1H), 4.53(m, 1H), 5.16(m, 1H), 8.63(d, 1H), 9.43(d, 1H), 9.81(s, 1H)

5 **Example 96 :** 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-*N*-[1-(hydroxymethyl)propyl]nicotinamide **·HCl**

By the same procedure as described in the example 94, the synthesis was carried out using *DL*-2-amino-1-butanol.

Yield: 69 %

10 ¹H-NMR(TFA-*d*₁), ppm : δ 1.21(t, 3H), 1.93(m, 2H), 3.78(m, 4H), 4.01(m, 1H), 4.22(m, 4H), 4.43(m, 1H), 4.53(m, 1H), 5.15(m, 1H), 8.63(d, 1H), 9.43(d, 1H), 9.80(s, 1H)

15 **Example 97 :** *N*-[2-hydroxy-1-(hydroxymethyl)ethyl]-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide **·HCl**

By the same procedure as described in the example 94, synthesis was carried out using 2-amino-1,3-propandiol.

Yield: 64 %

20 ¹H-NMR(TFA-*d*₁), ppm : δ 3.67(m, 4H), 4.11~4.25(m, 8H), 4.43(m, 3H), 4.53(m, 1H), 5.22(m, 1H), 8.63(d, 1H), 9.43(d, 1H), 9.81(s, 1H)

Example 98 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-*N*-(2-methoxyethyl)nicotinamide **·HCl**

25 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinic acid methyl ester(3 g) was dissolved in methanol(18 ml) and with the addition of 2-methoxyethylamine(4 ml), the mixture was heated to reflux for 12 hours and concentrated under reduced pressure. The residue was chromatographed on column (hexane/methylene chloride/methanol = 7/4/1). The purified

solution was recovered and concentrated under reduced pressure, and was dissolved in isopropanol. To this solution, 2N-hydrochloride solution in isopropanol(4.4 ml) was added, and ether(20 ml) was added, and the mixture was stirred for 1 hour. The mixture was filtered, washed(ether) and dried to
5 give a desired compound of 3.05 g(yield: 80 %) as hydrochloride salt.

m.p. : 150~152°C

¹H-NMR(CDCl₃), ppm : δ 2.84~2.92(m, 7H), 3.13~3.30(m, 7H), 3.48(m, 1H), 3.57(m, 2H), 3.87(m, 1H), 4.31(m, 1H), 7.33(d, 1H), 7.95(m, 1H), 8.16(s, 1H), 8.64(s, 1H)

10

Example 99 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-(3-methoxypropyl)nicotinamide

By the same procedure as described in the example 93, synthesis was carried out using 3-methoxypropylamine.

15 Yield: 73 %

m.p. : 88~90°C

¹H-NMR(CDCl₃), ppm : δ 1.87(m, 2H), 2.63(m, 6H), 3.38(s, 3H), 3.56(m, 6H), 3.66(m, 2H), 3.86(m, 2H), 7.23(m, 1H), 7.68(d, 2H), 8.15(m, 1H), 8.89(d, 1H)

20

Example 100 : N,N-bis(2-methoxyethyl)-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide ·HCl

By the same procedure as described in the example 94, synthesis was carried out using bis(2-methoxyethyl)amine.

Yield: 58 %

25

¹H-NMR(TFA-*d*₁), ppm : δ 3.68(m, 3H), 3.76(m, 2H), 3.84(s, 6H), 3.94(m, 4H), 4.06(m, 1H), 4.15(m, 1H), 4.17(m, 6H), 4.41(m, 1H), 4.47(m, 2H), 5.19(m, 1H), 8.55(d, 1H), 9.08(d, 1H), 9.51(s, 1H)

Example 101 : N-(2,2-dimethoxyethyl)-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide

By the same procedure as described in the example 93, synthesis was carried out using 2,2-dimethoxyethylamine.

5 Yield: 65 %

m.p. : 107 ~ 109 °C

¹H-NMR(TFA-*d*₁), ppm : δ 3.78(m, 2H), 4.15(m, 3H), 4.23-4.45(m, 13H), 4.90(d, 1H), 5.09(m, 2H), 5.21(m, 1H), 8.67(d, 1H), 9.45(d, 1H), 9.87(s, 1H)

10 **Example 102 : 6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]-N-[2-(morpholin-4-yl)-ethyl]nicotinamide ·HCl**

By the same procedure as described in the example 94, synthesis was carried out using 4-(2-aminoethyl)morpholine.

Yield: 70 %

15 ¹H-NMR(TFA-*d*₁), ppm : δ 3.86(m, 4H), 4.01(m, 5H), 4.10(m, 1H), 4.22(m, 2H), 4.34 ~ 4.43(m, 7H), 4.54(m, 5H), 5.19(m, 1H), 8.60(d, 1H), 9.06(d, 1H), 9.51(s, 1H)

20 **Example 103 : N-(2-Furylmethyl)-6-[1-(2-hydroxyethyl)piperazin-4-yl-carbonyl]nicotinamide ·HCl**

By the same procedure as described in the example 94, synthesis was carried out using furfurylamine.

Yield: 64 %

25 ¹H-NMR(TFA-*d*₁), ppm : δ 3.69(m, 2H), 3.87(m, 4H), 4.23(m, 2H), 4.37(m, 4H), 4.54(m, 2H), 5.21(m, 1H), 7.78(m, 2H), 8.60(d, 1H), 9.01(d, 1H), 9.36(d, 1H), 9.51(s, 1H)

Experiment 1 : Inhibitory activities against HBV polymerase *in vitro*.

Recently, the inventors of the present invention have produced a recombinant HBV polymerase that is expressed from *E.coli* transformant, measured its enzyme activity and filed patent applications thereof [Korean Pat. Appl. Nos. 94-3918 and 96-33998].

5 The inventors have also established a method of measuring the reverse transcriptase activity of HBV polymerase *in vitro*. The fundamental principle is the same as the ELISA method, and after reacting the substrate with biotin- and DIG-modified nucleotide, a method of recognizing the polymerized substrate as anti-DIG antibody with peroxidase was used.

10 20 μ l of HBV polymerase, 20 μ l of reaction mixture and 20 μ l of test compound was mixed and reacted at 14°C ~ 30°C for 18 ~ 24 hours. Then, the inhibitory effect of the test compound against reverse transcriptase activity in the HBV polymerase was examined, compared with the results of control tests without the test compound.

15 The inhibitory activities of each test compound were shown in the following tables 1a~1g and table 2.

Table 1a

The inhibitory effects of reverse transcriptase(RT) enzyme activity of HBV.

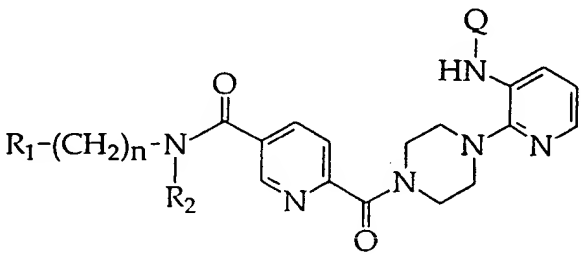
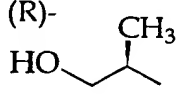
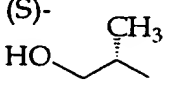
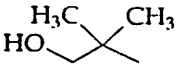
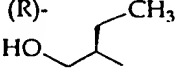
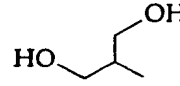
<div style="text-align: center;">  (1a) </div>							
Example	R ₁	R ₂	Q	n	Inhibitory activity of HBV-RT (%)		
					1 μg/ml	0.1 μg/ml	0.01 μg/ml
Exam. 1	HO-	H	<i>i</i> -Pr	2	54	51	30
Exam. 2	HO-	H	<i>i</i> -Pr	3	71	60	49
Exam. 3	(R)- 	H	<i>i</i> -Pr	0	74	57	41
Exam. 4	(S)- 	H	<i>i</i> -Pr	0	56	39	30
Exam. 6		H	<i>i</i> -Pr	0	80	65	62
Exam. 7	(R)- 	H	<i>i</i> -Pr	0	70	64	53
Exam. 13		H	<i>i</i> -Pr	0	72	56	51
Exam. 14	HO-	CH ₃ CH ₂ -	<i>i</i> -Pr	2	35	10	-
Exam. 16	HO-	HOCH ₂ CH ₂ -	<i>i</i> -Pr	2	70	60	51

Table 1b

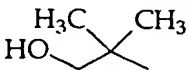
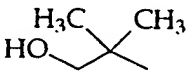
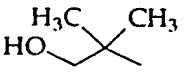
Example	R ₁	R ₂	Q	N	Inhibitory activity Of HBV-RT (%)		
					1 μ g/ml	0.1 μ g/ml	0.01 μ g/ml
Exam. 17	HO-	Ph-	<i>i</i> -Pr	2	66	53	42
Exam. 18	HO-	H	Et	2	84	69	52
Exam. 19		H	Et	0	72	56	32
Exam. 20	HO-	H	H	2	74	67	54
Exam. 21		H	H	0	70	62	38
Exam. 22	HO-	H	<i>i</i> -Bu	0	86	60	54
Exam. 23		H	<i>i</i> -Bu	0	90	71	63
Exam. 24	(CH ₃) ₂ CH-	H	<i>i</i> -Pr	0	65	51	23
Exam. 25	(CH ₃) ₂ CH-	H	Et	0	85	67	54
Exam. 26	(CH ₃) ₂ CH-	H	<i>i</i> -Bu	0	90	66	58
Exam. 27	(CH ₃) ₂ CH-	H	H	0	79	62	43
Exam. 28	(CH ₃) ₃ C-	H	<i>i</i> -Pr	0	88	72	61
Exam. 30	(CH ₃) ₂ CH-	H	<i>i</i> -Pr	1	83	65	61
Exam. 33	CH ₃ -	CH ₃ CH ₂ -	<i>i</i> -Pr	1	73	62	20

Table 1c



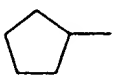
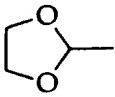
Example	R ₁	R ₂	Q	N	Inhibitory activity of HBV-RT (%)		
					1 μ g/ml	0.1 μ g/ml	0.01 μ g/ ml
Exam. 35		H	<i>i</i> -Pr	0	62	51	5
Exam. 36		H	<i>i</i> -Bu	0	87	71	60
Exam. 37		H	<i>i</i> -Pr	0	75	65	39
Exam. 39	CH ₃ O-	H	<i>i</i> -Pr	2	80	68	60
Exam. 40	CH ₃ O-	H	Et	2	75	57	36
Exam. 41	CH ₃ O-	H	<i>i</i> -Bu	2	85	70	52
Exam. 42	CH ₃ O-	CH ₃ O- (CH ₃) ₂ -	<i>i</i> -Pr	2	70	52	15
Exam. 43	CH ₃ OCH ₂ CH(CH ₃)-	H	<i>i</i> -Pr	0	68	61	50
Exam. 45	CH ₃ O-	H	<i>i</i> -Pr	3	63	53	28
Exam. 47	CH ₃ O-	H	<i>i</i> -Bu	3	72	51	20
Exam. 48	HO-(CH ₂) ₂ O-	H	<i>i</i> -Pr	2	79	66	52
Exam. 50	(CH ₃ O) ₂ CH-	CH ₃	<i>i</i> -Pr	1	60	51	15
Exam. 51	(CH ₃ O) ₂ CH-	H	<i>i</i> -Pr	1	87	65	57
Exam. 52		CH ₃	<i>i</i> -Pr	1	76	60	39

Table 1d

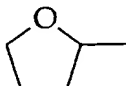
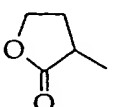
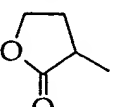
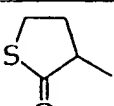
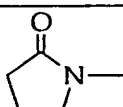
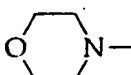
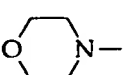
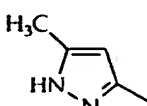
Example	R ₁	R ₂	Q	N	Inhibitory activity of HBV-RT(%)		
					1 μ g/ml	0.1 μ g/ml	0.01 μ g/ ml
Exam. 53		H	<i>i</i> -Pr	1	74	60	52
Exam. 55		H	<i>i</i> -Pr	0	79	69	55
Exam. 56		H	H	0	82	70	65
Exam. 57		H	<i>i</i> -Pr	0	72	53	23
Exam. 58		H	<i>i</i> -Pr	3	84	72	63
Exam. 59		H	<i>i</i> -Pr	2	70	60	49
Exam. 60		H	Et	2	66	52	30
Exam. 62	(CH ₃) ₂ N-	H	<i>i</i> -Pr	2	69	58	47
Exam. 66		H	<i>i</i> -Pr	0	70	53	20

Table 1e

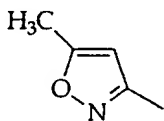
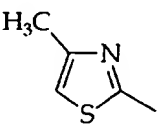
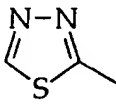
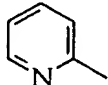
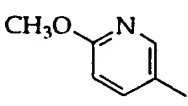
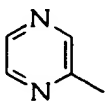
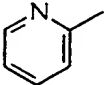
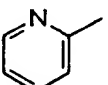
Example	R ₁	R ₂	Q	N	Inhibitory activity of HBV-RT(%)		
					1 μ g/ml	0.1 μ g/ml	0.01 μ g/ml
Exam. 67		H	<i>i</i> -Pr	0	72	50	25
Exam. 68		H	<i>i</i> -Pr	0	81	69	30
Exam. 69		H	<i>i</i> -Pr	0	64	47	12
Exam. 70		H	<i>i</i> -Pr	0	74	55	26
Exam. 71		H	<i>i</i> -Pr	0	83	70	59
Exam. 72		H	<i>i</i> -Pr	0	64	53	16
Exam. 73		H	<i>i</i> -Pr	1	77	62	53
Exam. 74		H	Et	1	70	56	19

Table 1f

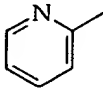
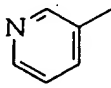
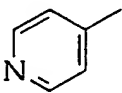
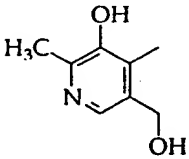

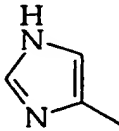
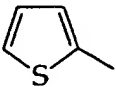
Example	R ₁	R ₂	Q	N	Inhibitory activity of HBV-RT(%)		
					1 μ g/ml	0.1 μ g/ml	0.01 μ g/ml
Exam. 75		H	H	1	72	54	22
Exam. 76		H	<i>i</i> -Pr	1	62	53	30
Exam. 77		H	<i>i</i> -Pr	1	79	65	39
Exam. 78		H	<i>i</i> -Pr	1	62	58	15
Exam. 79		H	<i>i</i> -Pr	1	78	63	54
Exam. 80		H	<i>i</i> -Pr	2	70	61	52
Exam. 81		H	<i>i</i> -Pr	2	80	60	44

Table 1g

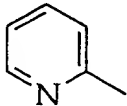
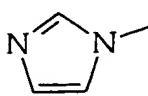
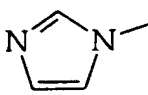
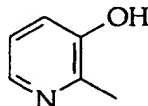
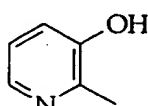
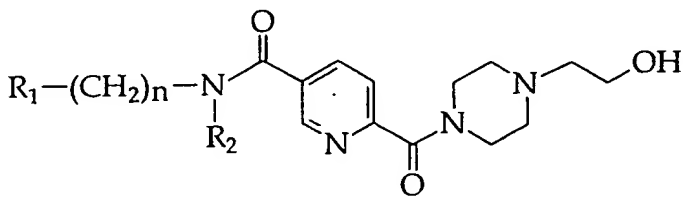
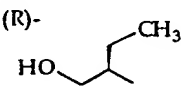
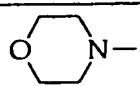
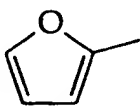
Example	R ₁	R ₂	Q	N	Inhibitory activity of BV-RT(%)		
					1 μ g/ml	0.1 μ g/ml	0.01 μ g/ml
Exam. 82		H	<i>i</i> -Pr	2	67	53	24
Exam. 83		H	<i>i</i> -Pr	3	89	72	65
Exam. 84		H	<i>i</i> -Bu	3	88	72	60
Exam. 85		H	<i>i</i> -Pr	0	88	70	61
Exam. 86		H	<i>i</i> -Bu	0	71	46	13

Table 2

<div style="text-align: center;">  (1b) </div>						
Example	R ₁	R ₂	n	Inhibitory activity of HBV-RT(%)		
				1 μg/ml	0.1 μg/ml	0.01 μg/ml
Exam. 87	(CH ₃) ₂ CH-	H	0	75	58	52
Exam. 88	(CH ₃) ₂ CH-	H	1	81	67	55
Exam. 89	CH ₃ -	H	1	68	50	35
Exam. 93	HO-	H	2	73	59	30
Exam. 94	(R)- 	H	0	72	51	20
Exam. 98	CH ₃ O-	H	2	85	70	57
Exam. 99	CH ₃ O-	H	3	68	60	15
Exam. 100	CH ₃ O-	CH ₃ OCH ₂ CH ₂ -	2	77	49	20
Exam. 101	(CH ₃ O) ₂ CH-	H	1	85	63	55
Exam. 102		H	2	70	56	32
Exam. 103		H	1	72	54	20

Experiment 2 : The *in vitro* inhibition test against HIV reverse transcriptase.

The inhibitory activity *in vitro* was measured using a non-radioactive reverse transcriptase assay Kit (Boehringer Mannheim).

At first, 20 μ l (40 ng) of HIV-RT was added to the wells, coated with streptavidin and with the addition of 20 μ l reaction mixture containing template/primer hybrid poly(A)/oligo(dT)₁₅ and DIG-(digoxigenin)-dUTP, biotin-dUTP and TTP, 20 μ l of test compound was added and reacted at 37°C for 1 hour. The control without test compound was used for the comparison of related activity. Since DNA containing nucleotide labeled with digoxigenin and biotine was prepared by the action of HIV-RT, it was combined with streptavidin coated at the bottom of the wells. After the reaction was completed, remaining impurities were removed by washing each well with 250 μ l buffer solution (pH 7.0) for 30 seconds 5 times and with the addition of 200 μ l anti-DIG-POD antibody, the mixture was reacted at 37°C for 1 hour. For the removal of remaining impurities again, the reacting solution was washed with a buffer solution and with the addition of 200 μ l ABTS™ each, a substrate of POD (peroxidase), the solution was reacted at room temperature for 30 minutes. The absorbance was read by ELISA reader at 405 nm for the assay of reverse transcriptase activity and its inhibition activity.

The results of inhibitory activities for each sample were shown in the following tables 3a~3f and table 4.

Table 3a

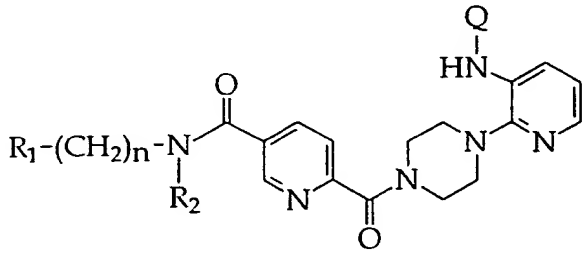
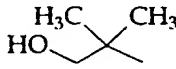
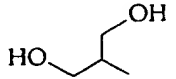

<div style="text-align: center;">  (1a) </div>						
Example	R ₁	R ₂	Q	N	Inhibitory activity of HIV-RT(%)	
					1 μg/ml	0.1 μg/ml
Exam. 6		H	<i>i</i> -Pr	0	70	48
Exam. 13		H	<i>i</i> -Pr	0	80	61
Exam. 16	HO-	HOCH ₂ CH ₂	<i>i</i> -Pr	2	68	47
Exam. 22	HO-	H	<i>i</i> -Bu	2	60	50
Exam. 23		H	<i>i</i> -Bu	0	62	46
Exam. 24	(CH ₃) ₂ CH-	H	<i>i</i> -Pr	0	66	30
Exam. 25	(CH ₃) ₂ CH-	H	Et	0	75	52
Exam. 26	(CH ₃) ₂ CH-	H	<i>i</i> -Bu	0	60	45
Exam. 27	(CH ₃) ₂ CH-	H	H	0	70	54
Exam. 28	(CH ₃) ₃ C-	H	<i>i</i> -Pr	0	55	45

Table 3b



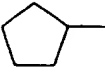
Example	R ₁	R ₂	Q	N	Inhibitory activity of HIV-RT(%)	
					1 μg/ml	0.1 μg/ml
Exam. 30	(CH ₃) ₂ CH-	H	<i>i</i> -Pr	1	58	32
Exam. 33	CH ₃ -	CH ₃ CH ₂ -	<i>i</i> -Pr	1	80	64
Exam. 35		H	<i>i</i> -Pr	0	68	30
Exam. 36		H	<i>i</i> -Bu	0	73	60
Exam. 37		H	<i>i</i> -Pr	0	51	25
Exam. 39	CH ₃ O-	H	<i>i</i> -Pr	2	72	65
Exam. 40	CH ₃ O-	H	Et	2	70	52
Exam. 41	CH ₃ O-	H	<i>i</i> -Bu	2	55	34
Exam. 42	CH ₃ O-	CH ₃ O- (CH ₂) ₂ -	<i>i</i> -Pr	2	54	20
Exam. 43	CH ₃ OCH ₂ CH(CH ₃)-	H	<i>i</i> -Pr	0	56	44
Exam. 45	CH ₃ O-	H	<i>i</i> -Pr	3	68	47
Exam. 47	CH ₃ O-	H	<i>i</i> -Bu	3	69	53
Exam. 48	HO-(CH ₂) ₂ O-	H	<i>i</i> -Pr	2	52	41
Exam. 50	(CH ₃ O) ₂ CH-	CH ₃	<i>i</i> -Pr	1	55	40

Table 3c

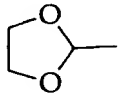
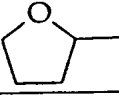
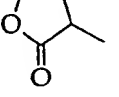
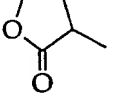
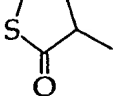
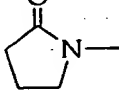
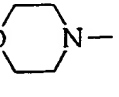
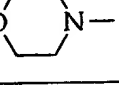
Example	R ₁	R ₂	Q	N	Inhibitory activity of HIV-RT(%)	
					1 μ g/ml	0.1 μ g/ml
Exam. 51	(CH ₃ O) ₂ CH-	H	<i>i</i> -Pr	1	51	30
Exam. 52		CH ₃	<i>i</i> -Pr	1	62	50
Exam. 53		H	<i>i</i> -Pr	1	78	59
Exam. 55		H	<i>i</i> -Pr	0	62	31
Exam. 56		H	H	0	74	45
Exam. 57		H	<i>i</i> -Pr	0	70	61
Exam. 58		H	<i>i</i> -Pr	3	63	45
Exam. 59		H	<i>i</i> -Pr	2	61	15
Exam. 60		H	Et	2	73	55
Exam. 62	(CH ₃) ₂ N-	H	<i>i</i> -Pr	2	79	63

Table 3d

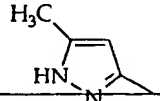
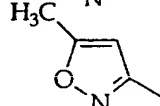
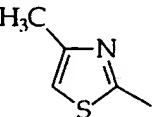
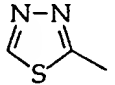
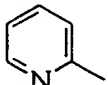
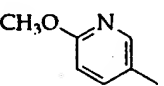

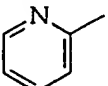
Example	R ₁	R ₂	Q	N	Inhibitory activity of HIV-RT(%)	
					1 μ g/ml	0.1 μ g/ml
Exam. 66		H	<i>i</i> -Pr	0	76	52
Exam. 67		H	<i>i</i> -Pr	0	58	30
Exam. 68		H	<i>i</i> -Pr	0	70	53
Exam. 69		H	<i>i</i> -Pr	0	67	35
Exam. 70		H	<i>i</i> -Pr	0	74	55
Exam. 71		H	<i>i</i> -Pr	0	74	48
Exam. 72		H	<i>i</i> -Pr	0	83	66
Exam. 73		H	<i>i</i> -Pr	1	73	57

Table 3e

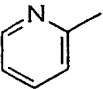
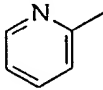
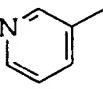
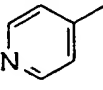
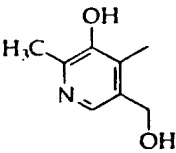
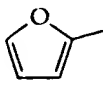
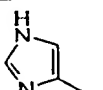
Example	R ₁	R ₂	Q	N	Inhibitory activity of HIV-RT(%)	
					1 μ g/ml	0.1 μ g/ml
Exam. 74		H	Et	1	80	61
Exam. 75		H	H	1	72	53
Exam. 76		H	<i>i</i> -Pr	1	82	57
Exam. 77		H	<i>i</i> -Pr	1	79	59
Exam. 78		H	<i>i</i> -Pr	1	70	52
Exam. 79		H	<i>i</i> -Pr	1	54	20
Exam. 80		H	<i>i</i> -Pr	2	48	21

Table 3f

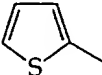
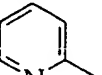
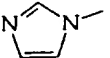
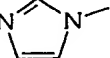
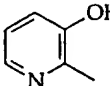
Example	R ₁	R ₂	R ₃	N	HIV-RT inhibitory activity (%)	
					1 μ g/ml	0.1 μ g/ml
Exam. 81		H	<i>i</i> -Pr	2	75	54
Exam. 82		H	<i>i</i> -Pr	2	80	65
Exam. 83		H	<i>i</i> -Pr	3	62	30
Exam. 84		H	<i>i</i> -Bu	3	62	50
Exam. 85		H	<i>i</i> -Pr	0	70	47

Table 4

$ \begin{array}{c} \text{R}_1-(\text{CH}_2)_n-\text{N}(\text{R}_2)-\text{C}(=\text{O})-\text{C}_6\text{H}_4-\text{C}(=\text{O})-\text{N}(\text{CH}_2)_2\text{N}(\text{CH}_2)_2\text{OH} \\ \text{(1b)} \end{array} $					
Example	R ₁	R ₂	N	Inhibitory activity of HIV-RT(%)	
				1 μg/ml	0.1 μg/ml
Exam. 87	(CH ₃) ₂ CH-	H	0	81	60
Exam. 88	(CH ₃) ₂ CH-	H	1	70	50
Exam. 89	CH ₃ -	H	1	62	35
Exam. 93	HO-	H	2	50	25
Exam. 94	$ \begin{array}{c} \text{CH}_3 \\ \\ \text{(R)-HO-CH}_2\text{-CH} \end{array} $	H	0	62	30
Exam. 98	CH ₃ O-	H	2	76	61
Exam. 99	CH ₃ O-	H	3	75	65
Exam. 100	CH ₃ O-	CH ₃ OCH ₂ CH ₂ -	2	64	40
Exam. 101	(CH ₃) ₂ CH-	H	1	56	41
Exam. 102	$ \begin{array}{c} \text{O} \\ \\ \text{N-} \end{array} $	H	2	40	25
Exam. 103	$ \begin{array}{c} \text{O} \\ \\ \text{C} \end{array} $	H	1	80	65

Experiment 3 : Cytotoxicity test

The cytotoxicity test was carried out using HepG2 cell *in vitro*. As a result, 2,5-pyridinedicarboxylic acid derivatives and its pharmaceutically acceptable salts proven not to have cytotoxicity with $CC_{50} \geq 200 \mu M$, thus
5 being quite effective in terms of safety.

As discussed in the above, the compounds of the formula 1 according to the present invention, and its pharmaceutically acceptable salts are effective as active ingredients of inhibiting the proliferation of retrovirus including HBV and HIV in that without any cytotoxicity.

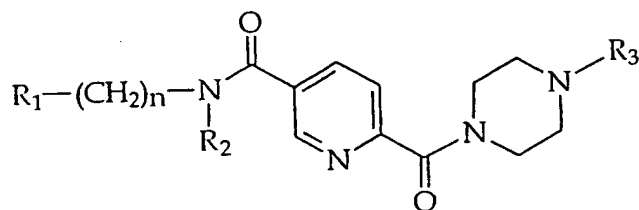
CLAIMS

What is claimed is:

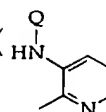
1. A 2,5-Pyridinedicarboxylic acid derivative of the following formula 1:

Formula 1

5



- wherein, R₁ represents hydroxy group, straight or branched alkyl
 10 group of 1 to 6 carbon atoms, cycloalkyl group of 3 to 6 carbon atoms
 unsubstituted or substituted with alkyl group of 1 to 3 carbon atoms, alkyl
 group of 1 to 3 carbon atoms substituted with cycloalkyl group of 3 to 6 carbon
 atoms, straight or branched hydroxyalkyl group of 1 to 6 carbon atoms ,
 straight or branched dihydroxyalkyl group of 3 to 6 carbon atoms, straight or
 15 branched alkoxy group of 1 to 4 carbon atoms, hydroxyalkoxy group of 2 to 4
 carbon atoms, straight or branched alkoxyalkyl group of 2 to 6 carbon atoms,
 dialkoxyalkyl group of 3 to 6 carbon atoms, dialkylamino group of 2 to 4
 carbon atoms, acetyl amino group, vinyl group, or saturated or unsaturated
 five or six membered heterocyclic ring having 1 to 3 hetero-atoms selected
 20 from the group consisting of nitrogen, oxygen and sulfur; hence, the
 heterocycle is unsubstituted or substituted with same or different 1~3
 substituents selected from the group consisting of alkyl group of 1 to 3 carbon
 atoms, alkoxy group of 1 to 3 carbon atoms, hydroxyalkyl group of 1 to 3
 carbon atoms, phenyl group, carbamoyl group and hydroxy group;
 25 R₂ represents hydrogen atom, phenyl group, straight or branched alkyl
 group of 1 to 4 carbon atoms, straight or branched hydroxyalkyl group of 2 to
 4 carbon atoms, or alkoxyalkyl group of 2 to 4 carbon atoms;

R_3 represents 3-amino-2-pyridyl group ()

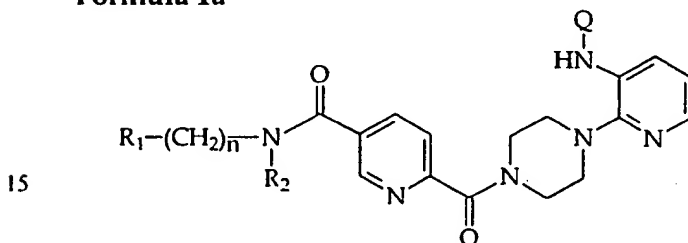
wherein, Q is hydrogen atom or straight or branched alkyl group of 1 to 4 carbon atoms), or 2-hydroxyethyl group;

5 n is an integer of 0 or 1~4;

meantime, the above R_1 that belong to branched hydroxyalkyl group may represent (*R*)- or (*S*)-type stereospecificity; or its pharmaceutically acceptable salts.

10 2. The 2,5-Pyridinedicarboxylic acid derivative according to claim 1, wherein said compound is of the following formula 1a:

Formula 1a



wherein, R_1 , R_2 , Q and n are the same, respectively as defined in said claim 1.; or its pharmaceutically acceptable salts.

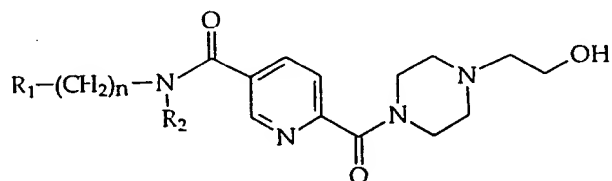
20 3. The 2,5-Pyridinedicarboxylic acid derivative according to claim 2, wherein said compound represents that R_1 is hydroxy group, branched hydroxyalkyl group of 3 to 5 carbon atoms, or branched dihydroxyalkyl group of 3 to 5 carbon atoms ; R_2 is hydrogen atom, methyl group, ethyl group, 2-hydroxyethyl group or phenyl group; n is 0, 2 or 3.; or its pharmaceutically
25 acceptable salts.

4. The 2,5-Pyridinedicarboxylic acid derivative according to claim 2, wherein said compound represents that R_1 is straight or branched alkyl group

of 2 to 4 carbon atoms, cyclopropyl group, cyclopentyl group, methoxy group, ethoxy group, 2-hydroxyethoxy group, branched alkoxyalkyl group of 4 to 5 carbon atoms, a dialkoxyalkyl group of 3 to 5 carbon atoms or dialkylamino group of 2 to 4 carbon atoms ; R_2 is hydrogen atom, methyl group, ethyl group, isopropyl group or 2-methoxyethyl group; n is an integer of 0 or 1~3.; or its pharmaceutically acceptable salts.

5. The 2,5-Pyridinedicarboxylic acid derivative according to claim 1, wherein said compound is of the following formula 1b:

10 **Formula 1b**

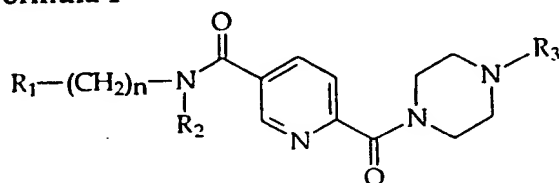


wherein, R_1 , R_2 and n are the same as defined in said claim 1.; or its pharmaceutically acceptable salts.

6. The 2,5-Pyridinedicarboxylic acid derivative according to claim 5, wherein said R_2 is hydrogen atom ; R_1 is straight or branched alkyl group of 2 to 4 carbon atoms, or straight or branched alkoxyalkyl group 2 to 5 carbon atoms ; n is 0 ; or its pharmaceutically acceptable salts.

7. A pharmaceutical composition that is effective as anti-retroviral agents containing 2,5-pyridinedicarboxylic acid derivatives of the following formula 1, or its pharmaceutically acceptable salts as an active ingredient:

25 **Formula 1**

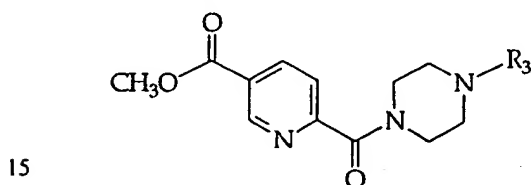


wherein, R_1 , R_2 and R_3 are the same, respectively as defined in said claim 1.

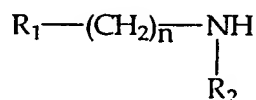
9. The pharmaceutical composition according to claim 7, wherein said
5 retrovirus represents hepatitis B virus(HBV) or human immunodeficiency virus(HIV)

9. A process for preparing 2,5-pyridinedicarboxylic acid derivative of the
following formula 1, comprising step of reacting nicotinic acid ester
10 derivatives of the following formula 2 and amine compounds of the following formula 3:

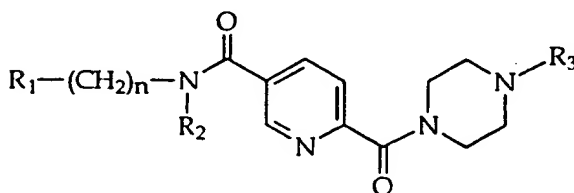
Formula 2



Formula 3



20 **Formula 1**



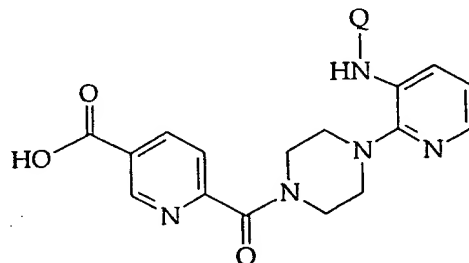
25 wherein, R_1 , R_2 , R_3 and n are the same as defined in said claim 1, respectively.

10. A process for preparing 2,5-pyridinedicarboxylic acid derivatives of the

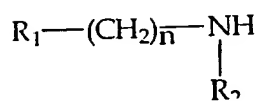
following formula 1a, comprising reacting of the compound of formula 2a, reactive intermediate of nicotinic acid derivative, with amine compounds of the following formula 3 :

Formula 2a

5

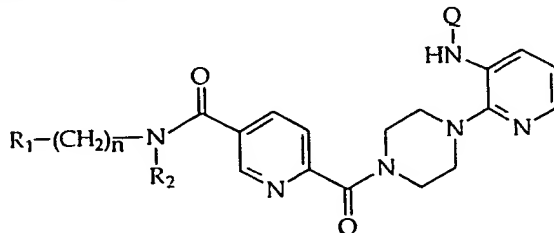


10 Formula 3



Formula 1a

15



wherein, R_1 , R_2 , Q and n are the same, respectively as defined in said

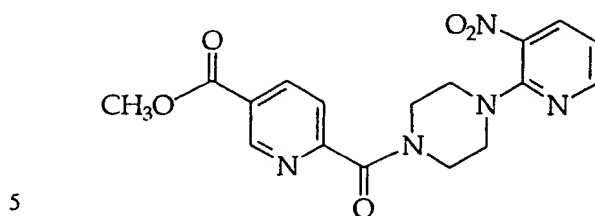
20 claim 1.

10. A process for preparing 2,5-pyridinedicarboxylic acid derivative of the following formula 1a comprising the steps of :

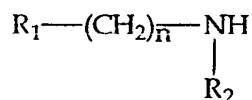
25 reaction of nicotinic acid ester derivative including nitropyridyl group with amine compound of the following formula 3 to form the intermediate of the following formula 6 ;

reduction of the intermediate or reductive alkylation after reduction of the intermediate.

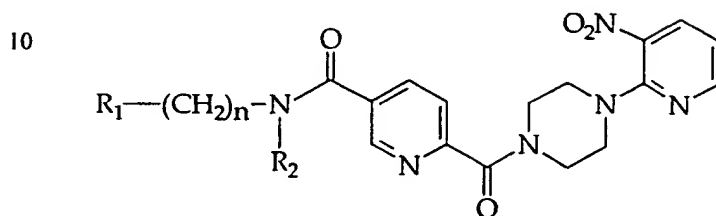
Formula 4



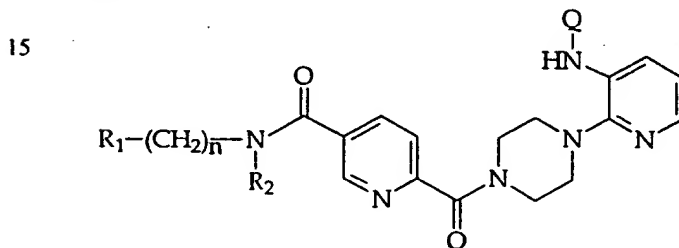
Formula 3



Formula 6



Formula 1a



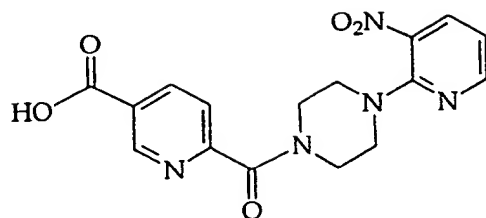
wherein, R_1 , R_2 , Q and n are the same, respectively as defined in said
 20 claim 1.

11. A process for preparing 2,5-pyridinedicarboxylic acid derivative of the following formula 1a comprising the steps of :

reaction of nicotinic acid ester derivative including nitropyridyl group
 25 of the following formula 5 with amine compound of the following formula 3,
 to form the intermediate of the following formula 6 ;

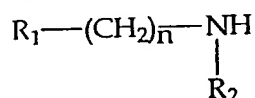
reduction of the intermediate or reductive alkylation after reduction of the intermediate.

Formula 5

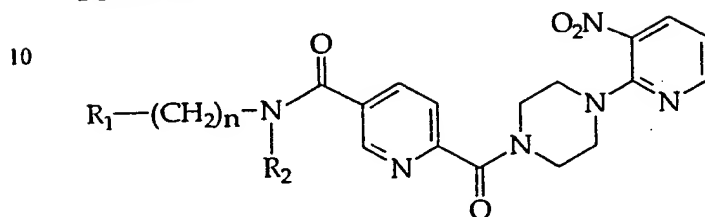


5

Formula 3

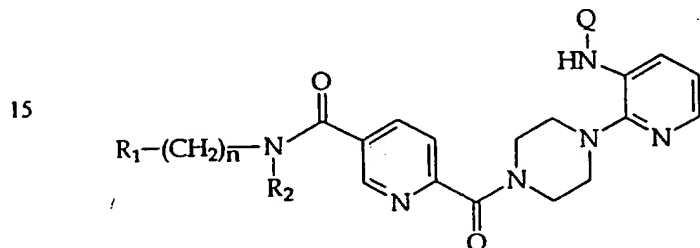


Formula 6



10

Formula 1a



15

wherein, R_1 , R_2 , Q and n are the same, respectively as defined in said claim 1.

20

13. A process for preparing nicotinic acid derivative of the following formula 2a comprising the steps of:

reaction of 5-(methoxycarbonyl)-2-pyridinecarboxylic acid of the following formula 7 with acid chloride derivative to form acid anhydride derivative; then, the reaction mixture is further reacted with 1-(3-nitro-2-pyridyl)piperazine of the following formula 8 to form nicotinic acid ester derivative including nitropyridyl group of the formula 4;

25

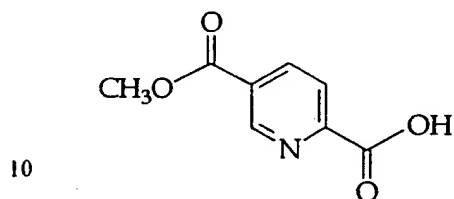
reduction of the compound of the formula 4 to obtain derivative

including aminopyridyl group of the formula 9;

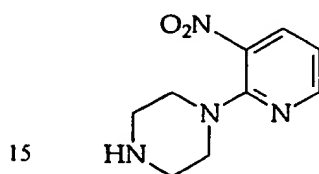
reductive alkylation of the derivative including aminopyridyl group of the formula 9 in the presence of reducing agent under acidic conditions to obtain nicotinic acid ester derivative of the following formula 2b; and,

5 hydrolysis of the nicotinic acid ester derivative of the formula 2b to give nicotinic acid derivative of the following formula 2a.

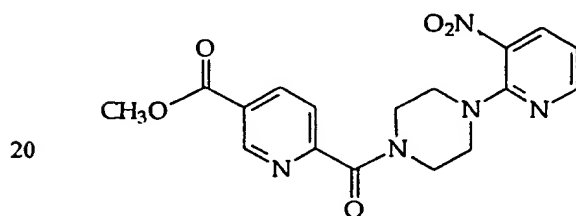
Formula 7



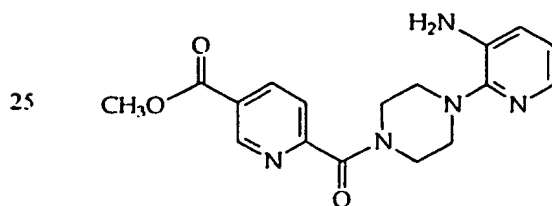
Formula 8



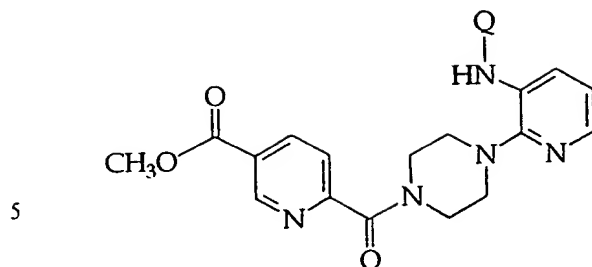
Formula 4



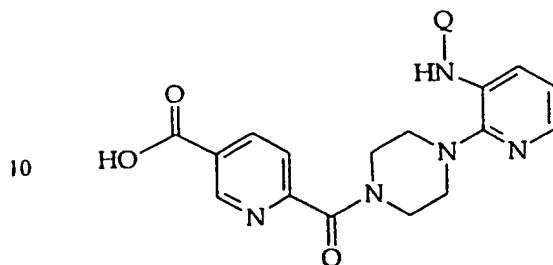
Formula 9



Formula 2b



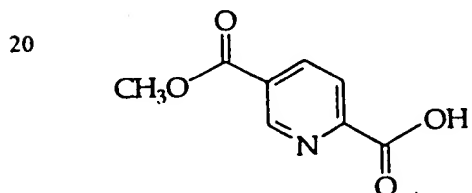
Formula 2a



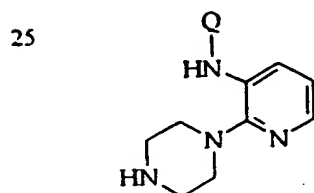
wherein, Q is the same as defined in said claim 1.

- 15 14. A process for preparing ester derivative of the following formula 2b ,
comprising reaction of 5-(methoxycarbonyl)-2-pyridinecarboxylic acid of the
following formula 7 with 1-[3-(alkylamino)-2-pyridyl]piperazine of the
following formula 10:

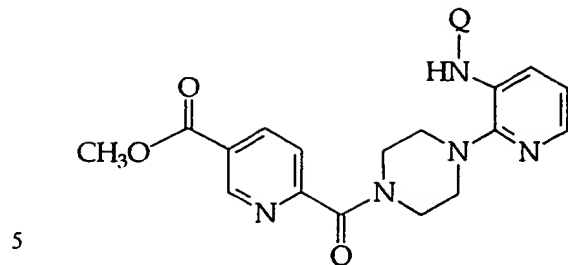
Formula 7



Formula 10



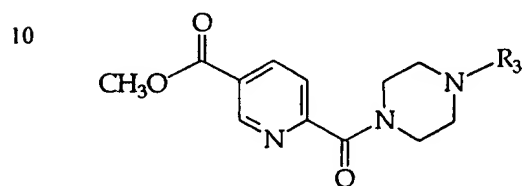
Formula 2b



wherein, Q is the same as defined in said claim 1.

15. Nicotinic acid ester derivative of the following formula 2:

Formula 2



wherein, R₃ is the same, respectively as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00213

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: C 07 D 401/14, 405/14, 409/14, 413/14, 417/14; A 61 K 31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: C 07 D 401/14, 405/14, 409/14, 413/14, 417/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS; EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 37 03 963 A1 (HOECHST), 18 August 1988 (18.08.88), claim 1; example 8.	1,15
A	DE 24 27 503 A1 (BANYU PHARM. CO.), 02 January 1976 (02.01.76), examples 11,12.	1,14,15
A	WO 98/03 503 A1 (FOURNIER IND ET SANTE), 29 January 1998 (29.01.98), claims 1,4,6; examples 67-70.	1-6,9-13
A	WO 97/26 880 A1 (PHARMACIA & UPPJOHN COMP.), 31 July 1997 (31.07.97), claim 9.	7.8
A	WO 96/06 082 A1 (PFIZER PHARM.), 29 February 1996 (29.02.96), claim 13.	7.8
A	WO 91/01 724 A1 (G. D. SEARLE & CO.), 21 February 1991 (21.02.91), claim 47.	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- ..A* document defining the general state of the art which is not considered to be of particular relevance
- ..E* earlier application or patent but published on or after the international filing date
- ..L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- ..O* document referring to an oral disclosure, use, exhibition or other means
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- ..X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- ..&* document member of the same patent family

Date of the actual completion of the international search

11 June 1999 (11.06.99)

Date of mailing of the international search report

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Authorized officer

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 99/00213

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
DE A1 3703963	18-08-1988	AT E 123022 AU A1 11450/88 AU B2 600084 DE C0 3853839 DK A0 660/88 DK A 660/88 DK A 909/92 DK A0 909/92 DK B1 168379 DK B1 170245 EP A2 278452 EP A3 278452 EP B1 278452 ES T2 2073393 FI A0 880554 FI A 880554 FI B 91524 FI C 91524 HU A2 47249 HU B 207295 IE B 67446 IL A0 85361 IL A1 85361 JP A2 63216870 KR B1 9611371 NO A0 880556 NO A 880556 NO B 173184 NO C 173184 NZ A 223431 PT A 66734 PT B 66734 US A 5238948 US A 5364873 ZA A 8800897	15-06-1995 11-08-1988 02-08-1990 29-06-1995 09-02-1988 11-08-1988 10-07-1992 10-07-1992 21-03-1994 17-07-1995 17-08-1988 18-10-1989 24-05-1993 16-08-1995 08-02-1988 11-08-1988 31-03-1994 11-07-1994 28-02-1989 29-03-1993 03-04-1996 31-07-1988 31-01-1993 09-09-1988 22-08-1996 09-02-1988 11-08-1988 02-08-1993 10-11-1993 26-07-1990 01-03-1988 29-05-1992 24-08-1993 15-11-1994 28-09-1988
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International Bureau(43) International Publication Date
18 November 1999 (18.11.1999)

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1998/28258 14 July 1998 (14.07.1998) KR(71) Applicant (for all designated States except US): DONG
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[KR/KR]; 2541-1, Keumkwang-2dong, Joongwon-ku,
Sungnam, Kyungki-do 462-242 (KR). PARK, Sang,
Jin [KR/KR]; 316, Keumho Apt., 44, Cheonho-1dong,
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[KR/KR]; 68-79, Bakdal-dong, Manan-ku, Anyang,
Kyungki-do 435-010 (KR). SIN, Dong, Hyuk [KR/KR];
402-2003, Jookong Apt., 885, Dang-dong, Kunpo,
Kyungki-do 435-010 (KR). CHANG, Hwan, Bong
[KR/KR]; 12/1, 135-7, Bupyung-2dong, Bupyung-ku,
Inchon 403-012 (KR).(74) Agent: HUH, Sang, Hoon; Hyecheon Building, 13th floor,
Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR).(81) Designated States (national): AL, AU, BA, BB, BG, BR,
CA, CN, CU, CZ, EE, GB, GD, GE, HR, HU, ID, IL, IN,
IS, JP, KP, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO,
NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN,
YU.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT,
BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,
GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(48) Date of publication of this corrected version:

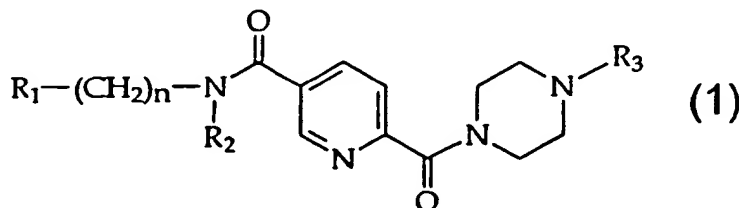
8 March 2001

(51) Information about Correction:

see PCT Gazette No. 10/2001 of 8 March 2001, Section II

[Continued on next page]

(54) Title: NOVEL 2,5-PYRIDINEDICARBOXYLIC ACID DERIVATIVES

(57) Abstract: The present invention relates to novel 2,5-pyridinedicarboxylic acid derivatives and more particularly, to novel 2,5-pyridinedicarboxylic acid derivatives of formula (1) and its pharmaceutically acceptable salts as anti retroviral agents, having inhibitory activities against the proliferation of retrovirus such as hepatitis B virus and human immunodeficiency virus, including its preparing method, wherein, R_1 , R_2 , R_3 and n are the same as defined in the detailed description of the invention, respectively.

WO 99/58526 A1

WO 99/58526 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.